A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Parallel Group, Multicenter Study With an Open-Label Extension to Evaluate the Efficacy and Safety of Ravulizumab in Patients With Amyotrophic Lateral Sclerosis (ALS)

Unique Protocol ID:	ALXN1210-ALS-308
NCT Number:	NCT04248465
EudraCT Number:	2019-004619-30
Date of Protocol:	23 June 2021

TITLE PAGE

Protocol Title: A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Parallel Group, Multicenter Study with an Open-Label Extension to Evaluate the Efficacy and Safety of Ravulizumab in Patients With Amyotrophic Lateral Sclerosis (ALS)

Protocol Number: ALXN1210-ALS-308

Amendment Number: 6

Compound: Ravulizumab (ALXN1210)

Study Phase: 3

Short Title: An Efficacy and Safety Study of Ravulizumab in ALS Patients

Sponsor Name: Alexion Pharmaceuticals, Inc.

Legal Registered Address: 121 Seaport Boulevard, Boston, MA 02210, USA

Regulatory Agency Identifier Numbers:

EudraCT Number: 2019-004619-30

IND Number: 145660

Approval Date: 23 Jun 2021

Sponsor Signatory:

PPD

04-Aug-2021 | 13:09:29 EDT

PPD MD, PhD
Executive Medical Director
Alexion Pharmaceuticals, Inc.

Date

Medical Monitor Contact Information can be found in the Study Contact List distributed to study sites.

Investigator's Agreement

I have read the ALXN1210-ALS-308 study protocol and agree to conduct the study in accordance with this protocol, all applicable government regulations, the principles of the ICH E6 Guidelines for Good Clinical Practice, and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 6 (Global)	23 Jun 2021

Amendment 6 (Global) (23 Jun 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The complete protocol amendment history is described in Section 10.16, Appendix 16.

Overall Rationale for the Amendment:

The main purposes of this amendment are:

- To allow patients to switch from the 10 mg/mL formulation to the 100 mg/mL formulation of ravulizumab with no change to the weight-based dose regimen at or after Week 52 in the Open-Label Extension Period
- To remove the second planned interim analysis

Other changes are presented in the table below.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Added the content below to the Overall Design: Patients may be allowed to switch from the 10 mg/mL to the 100 mg/mL formulation of ravulizumab with no change to the weight-based dose regimen at or after Week 52 in the OLE Period.	To provide the overall description that allows patients to switch from the 10 mg/mL to the100 mg/mL formulation of ravulizumab during the OLE Period.
1.1 Synopsis; 4 Objectives and Endpoints;	Change in the description of the endpoint from "Change from baseline in NfL concentration in serum at Week 50" to "NfL concentration in serum at Week 50."	Clarification in endpoint definition.
1.1 Synopsis; 1.2 Schema Figure 1; 3.1 Overall Design; 3.2.1 Study Population and Treatment Duration; 9.5 Interim Analysis	Change from 2 planned interim analyses to 1 planned interim analysis.	Due to faster than expected enrollment, the operational complexities associated with interim analysis 2 outweighed the anticipated gain in time in completing the Randomized-controlled Period due to early efficacy vs. full 50-week follow-up.

Section # and Name	Description of Change	Brief Rationale
1.2 Schema Figure 1; 3.1 Overall Design; 9.5 Interim Analysis	The following text has been added to provide clarity: "The study may be stopped if considered futile." The following text has been deleted as a result of this change: "The second interim analysis will be performed when approximately all patients have completed the Week 26 visit. At this time, a futility analysis will be conducted first. If the study is not considered futile, an analysis to determine early stopping for efficacy will be performed. If the efficacy analysis meets prespecified criteria, the Randomized Controlled Period may be stopped for success, and all patients in the Randomized Controlled Period may transition to the Open-Label Extension Period of the study."	The text has been altered to reflect the change from 2 to 1 interim analysis.
1.2 Schema, Figure 1; 1.3 Schedule of Activities, Tables 2 and 3	Added the following note to the footnotes: Note: Patients may be allowed to switch from the 10 mg/mL to the 100 mg/mL formulation of ravulizumab with no change to the weight-based dose regimen at or after Week 52 in the OLE Period.	To provide the description allowing patients to switch to the100 mg/mL formulation of ravulizumab in the OLE Period.
1.3.1 Screening to Week 50, Table 1	Changed assessment for ventilator utilization at Weeks 6, 14, and 22 from "in clinic" to allow that it can be performed "in clinic, by home visit, or by telephone contact". When performed by telephone, the telephone interview version of the questionnaire should be used, if available.	To allow for more flexibility in obtaining information on ventilator utilization.
1.3.2 Week 50 to 116, Table 2	Added collection of clinical laboratory tests at Week 52.	To correct inadvertent omission requiring collection of laboratory tests at Week 52.
3.1 Overall Design; 3.2.1 Study Population and Treatment Duration; 8.1.4.2 Open Label Extension Period	Added information that allows patients to switch from the 10 mg/mL to the 100 mg/mL formulation of ravulizumab with no change to the weight-based dose regimen at or after Week 52 in the OLE Period.	To provide study design of switch to the 100 mg/mL formulation of ravulizumab in the OLE Period.

Section # and Name	Description of Change	Brief Rationale
3.1 Overall Design 8.1.4 Study Drug Administration	The following text has been deleted: "In the event that the Randomized Controlled Period is stopped for success, any patient who is still in the Randomized Controlled Period will transition to the Open-Label Extension Period at their next scheduled dosing visit. Regardless of previous visit number, when the patient returns for the next scheduled dosing visit, the patient will follow the procedures outlined in Visit 13 in the SoA and continue all subsequent visits as outlined to the End of Study Visit. For patients who are in the Open-Label Extension Period when the Randomized Controlled Period is stopped for success, there will be no change to the visit schedule."	This text is deleted as a result of change to 1 interim analysis.
3.2.1 Study Population and Treatment Duration	The text below has been modified; text in **bold** has been added and text in ~~strikethrough~~ has been deleted. "A study design with **an** interim ~~analyses~~analysis was chosen to allow **consideration** for early stopping in the case of futility ~~or efficacy. The interim analyses~~, **which would** minimize ~~exposing patients~~the **duration of exposure** to an ineffective therapy ~~or prolonged exposure to placebo in the event of detecting efficacy earlier~~."	Provides rationale for a single interim analysis, and removes analysis to stop the study for efficacy.
3.2.1 Study Population and Treatment Duration	The following text has been added: "In this study patients may be allowed to switch from the 10 mg/mL to the 100 mg/mL formulation of ravulizumab with no change to the weight-based dose regimen during the OLE period. The 100 mg/mL IV formulation of ULTOMIRIS® (ravulizumab) was approved in 2020 by the FDA and the European Commission for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS). The 100 mg/mL ravulizumab is a higher concentration IV formulation which provides shorter preparation and infusion times while delivering comparable PK, safety and efficacy to the 10 mg/mL formulation of ravulizumab. Clinical data from Study ALXN1210-PNH-201 and Study ALXN1210-PNH-302 shows no change in the benefit/risk profile of ravulizumab following administration of the approved weight-based doses of ravulizumab using the 100 mg/mL formulation in patients with PNH."	To provide information supporting the benefit:risk of switching from the 10 mg/mL to the 100 mg/mL formulation, and provide current status of regulatory approval for the 100 mg/mL formulation.
4 Objectives and Endpoints; 9.4.5.3 Analysis of Exploratory Efficacy Endpoints	Any increase from baseline stage on the King's staging system at Week 50.	Clarification of endpoint language from "decline" to "increase".

Section # and Name	Description of Change	Brief Rationale
6.1 Study Drug(s) Administered, Table 5	Addition of 100 mg/mL formulation of ravulizumab.	To add in the 100 mg/mL formulation and to provide instruction on administering ravulizumab using the 100 mg/mL formulation.
6.5.2 Disallowed Medications and Therapies	Added the following text: "Note: Use of systemic corticosteroids for ≥ 14 days may be considered on a case-by-case basis in consultation with the Medical Monitor".	To correct an overly restrictive concomitant medication prohibition that is necessary neither for patient safety nor for treatment efficacy.
6.6 Dose Modification	Added the following **bold** text: Dose modification is not permitted for this study. **However, in the event of a missed or incomplete dose, and with the guidance of the Sponsor, supplemental dosing may be employed to maintain therapeutic steady state concentrations from disruptions in scheduled study drug dosing.**	Clarification added to address any potential missed or incomplete doses.
7.2 Patient Discontinuation/Withdrawal from the Study	Added collection of VAFS at End of Study/Early Discontinuation Visit.	Corrected omission, this is correct in the Schedule of Activities.
7.2 Patient Discontinuation/Withdrawal from the Study	The text below has been deleted: "This phone call can be omitted if it falls within 5 days of the ED visit."	Consistency with the footnotes in the Schedules of Activities
7.2 Patient Discontinuation/Withdrawal from the Study	Added a new bullet point: "If a patient withdraws from the study, the patient may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records as well as inform the site monitor and Sponsor."	Conformance with current protocol template and clarification for sample management.
8.2.2 Ventilation Assistance-Free Survival (VAFS)	The text below has been modified; text in **bold** has been added and text in ~~strikethrough~~ has been deleted. ~~Attempts~~**An attempt** will be made to obtain information about survival ~~even after~~ **at** the patient ~~has discontinued therapy~~**follow up phone call**.	Clarifies the timing for the final attempt to obtain assessment using the VAFS.

Section # and Name	Description of Change	Brief Rationale
9.1.2 Secondary Hypotheses	The secondary hypothesis "Change in ALSAQ-40 score" has been changed to "Neurofilament light chain concentration". The text below has been modified; text in **bold** has been added and text in ~~strikethrough~~ has been deleted. "4. ~~Change in ALSAQ-40 score~~ **Neurofilament light chain (NfL) concentration**: The alternative hypothesis is that treatment with ravulizumab ~~will show improvement in~~ lower ~~the change from baseline in ALSAQ-40~~ **NfL concentration** at Week 50 compared to placebo	To reflect secondary objectives as outlined in Section 4.
9.4.5.1.1 Primary Analysis 9.4.5.1.1.1 Alternate Primary analysis	The text below has been modified; text in **bold** has been added and text in ~~strikethrough~~ has been deleted. "A p-value less than the ~~adjusted~~Type I error ~~(Section)~~**= 0.05** associated with the higher mean rank in ravulizumab group compared to placebo will indicate a statistically significant treatment benefit	To reflect the omission of the interim analysis 2 for early efficacy.
9.4.5.1.1.1 Alternate Primary Analysis 9.4.5.1.2.1 Mixed-Effect Model for Repeated Measures (MMRM) Sensitivity Analysis 9.4.5.1.2.3 Vonesh Shared Parameter Model 9.4.5.2 Analyses of Secondary Efficacy Endpoints	The text in ~~strikethrough~~ below has been deleted: "In addition, the patient-specific random ~~intercept and~~ slope will be added to the model with an unstructured variance-covariance matrix to model the correlations among repeated measurements within each patient."	To reflect the change in the proposed statistical model.
9.4.5.2 Analysis of Secondary Efficacy Endpoints	The text indicated below in strikethrough has been deleted: ~~Change in~~ Neurofilament light chain concentration	Clarification in endpoint definition.

Abbreviations: NfL = neurofilament light chain; OLE = Open-Label Extension; SoA = Schedule of Activities; VAFS = ventilation assistance-free survival

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Parallel Group, Multicenter Study With an Open-Label Extension to Evaluate the Efficacy and Safety of Ravulizumab in Patients With Amyotrophic Lateral Sclerosis (ALS)

Short Title: An Efficacy and Safety Study of Ravulizumab in ALS Patients

Rationale:

Amyotrophic lateral sclerosis (ALS) is a debilitating neurodegenerative disease characterized by progressive degeneration of upper and lower motor neurons leading to severe disability and eventually death. Currently, riluzole and edaravone are the only available medications approved for the treatment of ALS that may slow disease progression. Management of ALS is otherwise supportive, palliative, and symptom based. Given the seriousness of the disease and limitations of the available treatments, there is a substantial unmet need for developing additional treatments that are efficacious and safe for patients with ALS.

The pathogenesis of ALS is largely unknown, but immune dysregulation and neuroinflammation have been implicated as potential mediators of disease. The therapeutic rationale for complement component 5 (C5) inhibition in ALS is supported by evidence of dysregulation of the complement system in tissue from patients with ALS. Furthermore, functional and survival benefits of C5 signaling blockade have been demonstrated in animal models of ALS. Ravulizumab (Ultomiris®) is a recombinant, humanized monoclonal antibody with high specificity for human C5. Ravulizumab has been shown to achieve immediate, complete, and sustained inhibition of terminal complement in adult patients with paroxysmal nocturnal hemoglobinuria (approved in the US, European Union, and Japan) and in pediatric and adult patients with atypical hemolytic uremic syndrome (approved in the US). It is expected that the same dosing regimen will also achieve comparable inhibition of complement-mediated damage in patients with ALS, which may slow ALS disease progression. The primary objective of this study is to investigate the efficacy and safety of ravulizumab in adult patients with ALS.

Objectives and Endpoints:

Objective	Endpoints
Primary	
To evaluate the effect of ravulizumab compared with placebo on amyotrophic lateral sclerosis functional rating scale-revised (ALSFRS-R) score in adult patients with amyotrophic lateral sclerosis (ALS)	Change from baseline in ALSFRS-R total score at Week 50
Secondary	
To evaluate the effect of ravulizumab compared with placebo on ventilation assistance-free survival (VAFS) in adult patients with ALS	Time to the earliest occurrence of 1 of the following events during the 50-week Randomized Controlled Period: • All-cause mortality • First use of non-invasive ventilation (NIV) for ≥ 22 hours per day for ≥ 10 consecutive days • First use of permanent assisted ventilation (PAV) for ≥ 22 hours per day for ≥ 7 consecutive days

Objective	Endpoints
To evaluate the effect of ravulizumab compared with placebo on respiratory function in adult patients with ALS	Change from baseline in percent (%) predicted slow vital capacity (SVC) at Week 50
To evaluate the safety of ravulizumab compared with placebo in adult patients with ALS	Incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and TEAEs leading to study drug discontinuation
To evaluate the effect of ravulizumab compared with placebo on muscle strength in adult patients with ALS	Percent change in combined muscle megascore from baseline at Week 50 as assessed by handheld dynamometry (HHD)
To evaluate the effect of ravulizumab compared with placebo on neurofilament light chain (NfL) concentrations in adult patients with ALS	NfL concentration in serum at Week 50
To characterize the pharmacokinetics (PK) of ravulizumab in adult patients with ALS	Change in serum ravulizumab concentration over the study duration
To characterize the pharmacodynamics (PD) of ravulizumab in adult patients with ALS	Change in serum free complement component 5 (C5) concentration over the study duration
To characterize the immunogenicity of ravulizumab in adult patients with ALS	Presence and titer of antidrug antibodies (ADAs)

Overall Design

Study ALXN1210-ALS-308 is a Phase 3, double-blind, randomized, placebo-controlled, parallel group, multicenter study to evaluate the efficacy and safety of ravulizumab in adult patients with ALS. There are 3 periods in this study: Screening Period, Randomized Controlled Period, and Open-Label Extension Period.

Patients will be screened for eligibility for up to 4 weeks during the Screening Period. Approximately 354 eligible adult patients with ALS from North America, Europe, and the Asia-Pacific region will be enrolled into the study. Patients who are not taking or who are on a stable regimen of riluzole and/or edaravone at screening will be considered for participation. Eligible patients will be randomized in a 2:1 ratio to receive weight-based intravenous (IV) infusion of ravulizumab or matching placebo until Week 50 during the double-blind Randomized Controlled Period. Randomization will be stratified based on the site of ALS muscle weakness onset (bulbar vs other) and background ALS treatment (riluzole and/or edaravone vs neither ALS therapy). For each patient, the Randomized Controlled Period ends and the Open-Label Extension Period starts when the patient has completed the Week 50 visit assessments. Regardless of prior treatment allocation, all patients will receive ravulizumab treatment during the Open-Label Extension Period. The Open-Label Extension Period will continue for up to 2 years, or until ravulizumab is approved and/or available (in accordance with country-specific regulations), whichever occurs first. Patients may be allowed to switch from the 10 mg/mL to the 100 mg/mL formulation of ravulizumab with no change to the weight-based dose regimen at or after Week 52 in the OLE Period. After the end of treatment visit or early discontinuation (ED), patients will be followed for an additional 8 weeks after their last dose of study drug. Treatment allocation will be blinded to patients, study site, the Sponsor, and the Sponsor's delegates throughout the Randomized Controlled Period. Blind to prior assignment will be maintained for patients and providers during the Open-Label Extension Period until end of the study.

One interim analysis for futility is planned during the Randomized Controlled Period. An independent data monitoring committee will be established to conduct the unblinded interim

analysis and periodic review of accumulating data for patient safety and efficacy during the study.

Disclosure Statement: This is a parallel group intervention study with 2 treatment arms followed by an Open-Label Extension Period.

Number of Patients:

Approximately 354 eligible adult patients will be enrolled.

Intervention Groups and Duration:

Eligible patients will be enrolled into the study and will be randomized in a 2:1 ratio to receive IV ravulizumab or placebo.

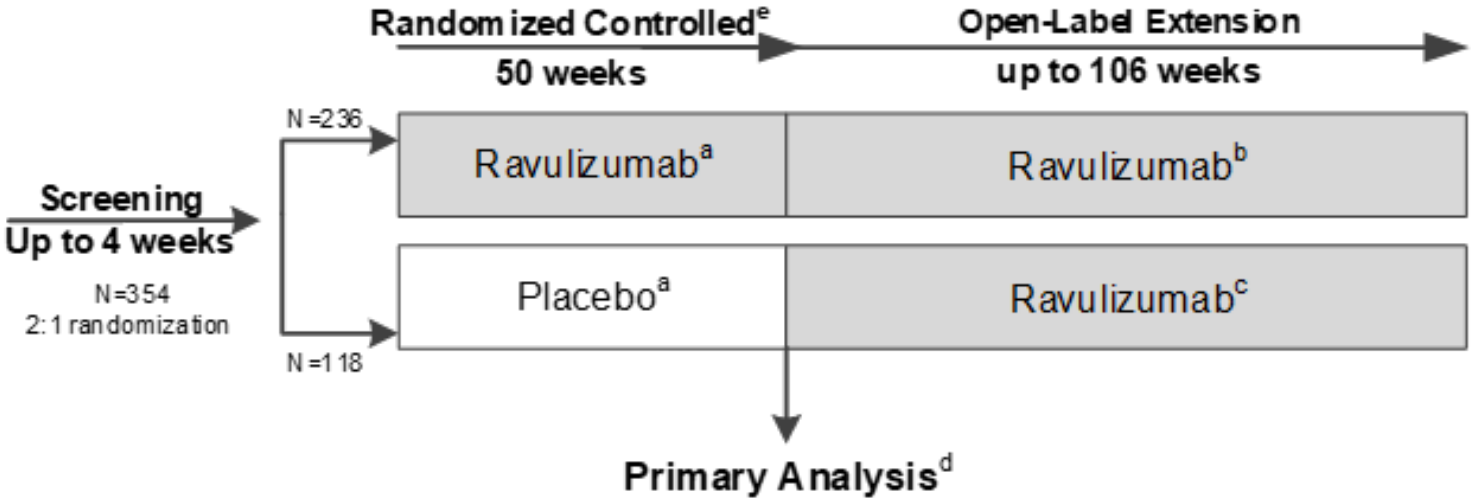
The study drug dose for each patient will be based on body weight. The dosing regimen consists of a loading dose followed by maintenance doses administered every 8 weeks (q8w). The maintenance dosing should be initiated 2 weeks after the loading dose administration.

For each patient, the total duration of study participation will be up to 160 weeks, including the Screening Period (up to 4 weeks), the Randomized Controlled Period (50 weeks), and the Open-Label Extension Period (up to 106 weeks).

Data Monitoring Committee: Yes

1.2. Schema

Figure 1: Study Design Schematic



Abbreviations: ALS = amyotrophic lateral sclerosis; PD = pharmacodynamics; PK = pharmacokinetics; q8w = every 8 weeks

[a] During the double-blind Randomized Controlled Period, patients will receive a weight-based loading dose of ravulizumab or matching placebo on Day 1, followed by a weight-based maintenance dose on Day 15, then q8w up to Week 42 (inclusive).

[b] During the Open-Label Extension Period, patients in the ravulizumab group will continue to receive ravulizumab, with a blinded 900 mg dose at Week 50, followed by an open-label ravulizumab maintenance dose at Week 52, then open-label ravulizumab maintenance doses q8w until the end of Open-Label Extension Period when all patients have completed up to 106 weeks of treatment or ravulizumab is approved and/or available (in accordance with country-specific regulations).

[c] During the Open-Label Extension (OLE) Period, patients in the placebo group will switch treatment to receive ravulizumab, with a blinded loading dose at Week 50, followed by an open-label maintenance dose at Week 52. Patients may be allowed to switch from the 10 mg/mL to the 100 mg/mL formulation of ravulizumab with no change to the weight-based dose regimen at or after Week 52 in the OLE Period. Patients will continue to receive open-label ravulizumab maintenance doses q8w until the end of the Open-Label Extension Period when all patients have completed up to 106 weeks of treatment or ravulizumab is approved and/or available (in accordance with country-specific regulations).

[d] The Randomized Controlled Period ends when all patients have completed the Week 50 visit. The primary analysis will be conducted based on the efficacy, safety, and PK/PD/immunogenicity data from the Randomized Controlled period to support the registration of ravulizumab for the treatment of ALS.

[e] One interim analysis for futility is planned during the Randomized Controlled Period (Section 9.5). The interim analysis for futility will be conducted when approximately 33% patients have completed the Week 26 (6 months) visit. The study may be stopped if considered futile.

1.3. Schedule of Activities (SoA)

1.3.1. Screening to Week 50

Table 1: Schedule of Activities: Screening to Week 50

Period	Screen-ing	Randomized Controlled Period												Notes
Visit[a]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12[b]**	**13**	Additional visits can be performed as needed. An ED Visit should be performed if patients discontinue early.
Week	**Up to 4 W**		**W2**	**W6**	**W10**	**W14**	**W18**	**W22**	**W26**	**W34**	**W42**	**W46**	**W50/ ED in RCP[c]**	
Days and Window		**D1**	**D15 ± 2**	**D43 ± 3**	**D71 ± 3**	**D99 ± 3**	**D127 ± 3**	**D155 ± 3**	**D183 ± 3**	**D239 ± 3**	**D295 ± 3**	**D323 ± 3**	**D351 ± 3**	
General Assessments/Procedures														
Informed consent	X													
Medical history	X													
ALS history/ diagnosis	X													
KSS	X								X				X	
Inclusion/ exclusion	X													
Demographics	X													
Weight[d]	X	X	X		X		X		X	X	X		X	
Height	X													
Neisseria meningitidis vaccination	X													Vaccination against meningococcal infection, and revaccination during the study if needed (Section 8.1.2).
HIV test	X													Including HIV-1 and HIV-2.

Table 1: Schedule of Activities: Screening to Week 50

Period	Screen-ing	Randomized Controlled Period												Notes
Visit[a]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12[b]**	**13**	
Week	**Up to 4 W**		**W2**	**W6**	**W10**	**W14**	**W18**	**W22**	**W26**	**W34**	**W42**	**W46**	**W50/ ED in RCP[c]**	Additional visits can be performed as needed. An ED Visit should be performed if patients discontinue early.
Days and Window		**D1**	**D15 ± 2**	**D43 ± 3**	**D71 ± 3**	**D99 ± 3**	**D127 ± 3**	**D155 ± 3**	**D183 ± 3**	**D239 ± 3**	**D295 ± 3**	**D323 ± 3**	**D351 ± 3**	
Pregnancy test (WOCBP only)	X	X	X		X		X		X	X	X		X	Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committees. Testing at indicated visits and when necessary at Investigator's discretion (Section 8.3.10).
General Assessments/Procedures														
Dispense patient safety card	X													Instruct patients to carry safety card at all times and bring it to the scheduled visits.
Efficacy Assessments														
ALSFRS-R[e,f]	X	X	X	H	X	H	X	H	X	X	X		X	Collect in clinic (X) or by phone (H)[h].
SVC[e,g]	X	X	X		X		X		X	X	X		X	Collect in clinic and at home[g]
HHD[e]		X			X				X				X	
Ventilator utilization	X	X	X	H	X	H	X	H	X	X	X	X	X	Collect in clinic (X) or by phone (H)[h].
ALSAQ-40	X	X							X				X	
EQ-5D-5L[f]	X	X	X	H	X	H	X	H	X	X	X		X	Collect in clinic (X) or by phone (H)[h].
SF-36	X	X							X				X	
TSQM		X							X				X	

Table 1: Schedule of Activities: Screening to Week 50

Period	**Screen -ing**	**Randomized Controlled Period**												**Notes**
Visit[a]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12[b]**	**13**	Additional visits can be performed as needed. An ED Visit should be performed if patients discontinue early.
Week	**Up to 4 W**		**W2**	**W6**	**W10**	**W14**	**W18**	**W22**	**W26**	**W34**	**W42**	**W46**	**W50/ ED in RCP[c]**	
Days and Window		**D1**	**D15 ± 2**	**D43 ± 3**	**D71 ± 3**	**D99 ± 3**	**D127 ± 3**	**D155 ± 3**	**D183 ± 3**	**D239 ± 3**	**D295 ± 3**	**D323 ± 3**	**D351 ± 3**	
Safety Assessments														
Neurologic examination	X								X				X	
Physical examination	X	X											X	An abbreviated physical examination can be performed at any visit after Day 1.
Vital signs	X	X	X		X		X		X	X	X		X	
ECG	X								X				X	
Prior medications and procedures	X													
Concomitant medications and procedures		Continuous monitoring												
AEs	Continuous monitoring													
Safety Assessments														
Clinical laboratory tests	X	X	X		X		X		X	X	X		X	Coagulation panel required at screening (W18, and W42 required only for patients in optional CSF cohort).
Patient safety card review		X	X		X		X		X	X	X		X	

Table 1: Schedule of Activities: Screening to Week 50

Period	Screen-ing	Randomized Controlled Period												Notes
Visit[a]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12[b]**	**13**	Additional visits can be performed as needed. An ED Visit should be performed if patients discontinue early.
Week	**Up to 4 W**		**W2**	**W6**	**W10**	**W14**	**W18**	**W22**	**W26**	**W34**	**W42**	**W46**	**W50/ ED in RCP[c]**	
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C-SSRS[e]		B			X		X		X	X	X		X	C-SSRS Screening/baseline version (B) to be performed at Day 1 and Since Last Visit version (X) at all other timepoints.
Pharmacokinetic and Pharmacodynamic Assessments														
Blood samples for PK/free C5		B/P	T/P		T/P		T/P		T/P	T/P	T/P		T	At ED visit, samples can be anytime.
Blood samples for ADA		B			T				T				T	At ED visit, samples can be anytime.
Biomarker Research														
Blood samples for biomarker		B	T		T				T	T			T	At ED visit, samples can be anytime.
Blood samples for DNA and RNA		B	T						T					Optional; collect samples from patients who consent to DNA and RNA collection. The blood sample for RNA is collected at all time points and the blood sample for DNA is collected on Day 1.[i]
Urine samples for biomarkers		X	X						X				X	

Table 1: Schedule of Activities: Screening to Week 50

Period	Screen-ing	Randomized Controlled Period												Notes
Visit[a]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12[b]**	**13**	Additional visits can be performed as needed. An ED Visit should be performed if patients discontinue early.
Week	**Up to 4 W**		**W2**	**W6**	**W10**	**W14**	**W18**	**W22**	**W26**	**W34**	**W42**	**W46**	**W50/ ED in RCP[c]**	
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CSF Cohort Sample Collection (Optional for Consenting Patients)														
CSF samples for PK/free C5 and biomarkers[j]	B							X				X		Participation in CSF cohort is optional; after consenting, samples are collected at all timepoints indicated.
Blood samples for PK/free C5 and biomarkers								X				X		
Administration of Study Drug														
Randomization		X												
Ravulizumab or placebo		X	X		X		X		X	X	X			Administer after all other required tests/procedures.

Note: B = baseline (Day 1); P = postdose; T = trough (predose); X = anytime.

Abbreviations: ADA = antidrug antibody; AE = adverse event; ALSAQ-40 = amyotrophic lateral sclerosis assessment questionnaire; ALSFRS-R = amyotrophic lateral sclerosis functional rating scale-revised; CBC = complete blood count; CSF = cerebrospinal fluid; C-SSRS = Columbia-suicide severity rating scale; ECG = electrocardiogram; ED = early discontinuation; EQ-5D-5L = European Quality of Life Health 5-item questionnaire; HHD = handheld dynamometry; KSS = King's staging system; PK = pharmacokinetics; RCP = Randomized Controlled Period; SF-36 = short form health survey; SVC = slow vital capacity; TSQM = Treatment Satisfaction Questionnaire for Medication; W = week; WOCBP = women of childbearing potential

[a] Under reasonable occasional circumstances where a patient is not able to attend a study visit on site, a home visit (where available) or visit at an alternative healthcare facility may be permitted by the Sponsor after discussing with the Alexion Medical Monitor (or delegate). This will be a case-by-case decision (Section 8.1.5).

[b] This visit is optional. It should be completed only by patients who consent to optional CSF collection.

[c] For patients who discontinue the study prior to the end of the Randomized Controlled Period, the ED in RCP visit should be completed as soon as possible. In addition, a Follow-up Phone Call will be performed 8 weeks (56 days) ± 5 days following the patient's last dose of study drug to collect concomitant medications, nonpharmacological therapies and procedures, VAFS, and AEs.

[d] Ravulizumab dosing is based on the last recorded study visit body weight. When possible, weights should be obtained at every dosing visit; consecutive weights must not be more than 16 weeks apart.

[e] Performed by the Investigator or any designee who has been properly trained and certified for the evaluation, preferably the same Investigator or designee, throughout the study. When possible, ALSFRS-R should be performed first, SVC second, and HHD should be performed as last assessment prior to dosing.

[f] At the time points specified, or if a patient is not able to attend the scheduled onsite visit, the ALSFRS-R and EQ-5D-5L can be assessed via a phone call by the Investigator or trained designee.

[g] In addition to SVC in the clinic, home SVC (where regionally available) should be performed using a provided spirometer and under the direction of study staff properly trained for the evaluation (Section 8.2.3). In the event that an SVC measurement cannot be obtained in the clinic due to the COVID-19 pandemic, only home evaluation is required for that visit. Home SVC at screening should be performed after informed consent and after the patient has received training on the spirometer. For subsequent visits, including Day 1, home SVC should be performed within 3 days prior to the scheduled clinic visit.

[h] Assessments denoted by H can be performed in clinic, by home visit, or by telephone contact. When performed by telephone, the telephone interview version of the questionnaire should be used, if available.

[i] If Day 1 sample collection is missed, the DNA sample can be collected at any scheduled visit thereafter.

[j] Most recent CBC and coagulation panel should be reviewed prior to CSF sample collection. Lumbar punctures must be performed after all assessments are completed and the investigator confirms the patient is eligible for randomization.

1.3.2. Week 50 to Week 116

Table 2: Schedule of Activities: Week 50 to Week 116

Period	Open-Label Extension Period										Notes
Visit[a]		**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	Additional visits can be performed as needed. An ED Visit should be performed if patients discontinue early (Table 3).
Week	**W50**	**W52**	**W60**	**W68**	**W76**	**W84**	**W92**	**W100**	**W108**	**W116**	
Days and Window	**D351 ± 3**	**D365 ± 3**	**D421 ± 7**	**D477 ± 7**	**D533 ± 7**	**D589 ± 7**	**D645 ± 7**	**D701 ± 7**	**D757 ± 7**	**D813 ± 7**	
General Assessments/Procedures											
Weight[b]		X	X	X	X	X	X	X	X		
Neisseria meningitidis vaccination											Patients must be vaccinated against meningococcal infection, and revaccinated during the study if needed (Section 8.1.2).
Pregnancy test (WOCBP only)		X	X	X	X	X	X	X	X	X	Urine test at indicated visits and when necessary at Investigator's discretion (Section 8.3.10).
Efficacy Assessments											
ALSFRS-R[c,d]		X	X	X	X	X	X	X	X	X	
SVC[c,e]			X		X		X		X		Collect in clinic and at home.[e] SVC at Visit 21 is optional, as patient condition permits.
Ventilator utilization		X	X	X	X	X	X	X	X	X	
EQ-5D-5L[d]		X	X	X	X	X	X	X	X	X	
Safety Assessments											
Neurologic examination					X						
Abbreviated physical examination											An abbreviated physical examination can be performed at any visit after Day 1.
Vital signs		X	X	X	X	X	X	X	X	X	
ECG							X				
Concomitant medications	Continuous monitoring										
AEs	Continuous monitoring										
Clinical laboratory tests		X		X		X		X		X	
Patient safety card review		X	X	X	X	X	X	X	X	X	
C-SSRS[e]				X		X		X	X		Perform C-SSRS since last visit assessment.
Pharmacokinetic and Pharmacodynamic Assessments											
Blood samples for PK/free C5	P	T/P	T/P			T/P			T/P		
Blood samples for ADA			T			T			T		

Table 2: Schedule of Activities: Week 50 to Week 116

Period	Open-Label Extension Period										Notes
Visit[a]		**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	Additional visits can be performed as needed. An ED Visit should be performed if patients discontinue early (Table 3).
Week	**W50**	**W52**	**W60**	**W68**	**W76**	**W84**	**W92**	**W100**	**W108**	**W116**	
Days and Window	**D351 ± 3**	**D365 ± 3**	**D421 ± 7**	**D477 ± 7**	**D533 ± 7**	**D589 ± 7**	**D645 ± 7**	**D701 ± 7**	**D757 ± 7**	**D813 ± 7**	
Biomarker Research											
Blood samples for biomarker			T			T			T		
Blood samples for DNA and RNA									T		Optional; samples collected from patients who consent to DNA and RNA collection. The blood sample for RNA is collected at all time points and the blood sample for DNA is collected on Day 1.[f]
Urine samples for biomarkers			X			X			X		
Administration of Study Drug											
Ravulizumab[h]	X[g]	X	X	X	X	X	X	X	X	X	Administer after all other required tests/procedures.

Note: P = postdose; T = trough (predose); X = anytime.

Abbreviations: ADA = antidrug antibody; AE = adverse event; ALSFRS-R = revised amyotrophic lateral sclerosis functional rating scale; C5 = complement component 5; C-SSRS = Columbia-suicide severity rating scale; D = day; ECG = electrocardiogram; ED = early discontinuation; EQ-5D-5L = European Quality of Life Health 5-item questionnaire; HHD = handheld dynamometry; PK = pharmacokinetics; SVC = slow vital capacity; W = week; WOCBP = women of childbearing potential

[a] Under reasonable occasional circumstances where a patient is not able to attend a study visit on site, a home visit (where available) or visit at an alternative healthcare facility may be permitted by the Sponsor after discussing with the Alexion Medical Monitor (or delegate). This will be a case-by-case decision (Section 8.1.5).

[b] Ravulizumab dosing is based on the last recorded study visit body weight. When possible, weights should be obtained at every dosing visit; consecutive weights must not be more than 16 weeks apart.

[c] Performed by the Investigator or any designee who has been properly trained and certified for the evaluation, preferably the same Investigator or designee, throughout the study. When possible, ALSFRS-R should be performed first, SVC second, and HHD should be performed as last assessment prior to dosing.

[d] If a patient is not able to attend the scheduled onsite visit, the ALSFRS-R and EQ-5D-5L can be assessed via a phone call by the Investigator or trained designee.

[e] In addition to SVC in the clinic, home SVC (where regionally available) should be performed using a provided spirometer and under the direction of study staff properly trained for the evaluation (Section 8.2.3). In the event that an SVC measurement cannot be obtained in the clinic due to the COVID-19 pandemic, only home evaluation is required for that visit. Home SVC at screening should be performed after informed consent and after the patient has received training on the spirometer. For subsequent visits, including Day 1, home SVC should be performed within 3 days prior to the scheduled clinic visit.

[f] If Day 1 sample collection is missed, the DNA sample can be collected at any scheduled visit thereafter.

[g] If this is an ED visit, no dose of study drug is given.

[h] Patients may be allowed to switch from the 10 mg/mL to the 100 mg/mL formulation of ravulizumab with no change to the weight-based dose regimen at or after Week 52 in the Open-Label Extension (OLE) Period (Section 3.1).

1.3.3. Week 124 to End of Study

Table 3: Schedule of Activities: Week 124 to End of Study

Period	**Open-Label Extension Period**					**Notes**
Visit[a]	**23**	**24**	**25**	**26**	**27**	Additional visits can be performed as needed. An ED Visit should be performed if patients discontinue early.
Week	**W124**	**W132**	**W140**	**W148/ EOT**	**W156/ EOS/ED in OLE**[b]	
Days and Window	**D869 ± 7**	**D925 ± 7**	**D981 ± 7**	**D1037 ± 7**	**D1093 ± 7**	
General Assessments/Procedures						
Weight[c]	X		X		X	
Neisseria meningitidis vaccination						Patients must be vaccinated against meningococcal infection, and revaccinated during the study if needed (Section 8.1.2).
Pregnancy test (WOCBP only)	X	X	X	X	X	Urine test at indicated visits and when necessary at Investigator's discretion (Section 8.3.10).
Efficacy Assessments						
ALSFRS-R[d,e]	X	X	X	X	X	
SVC[d,f]	X		X		X	Collect in clinic and at home.[f] Optional as patient's condition permits.
Ventilator Utilization	X	X	X	X	X	
EQ-5D-5L[e]	X	X	X	X	X	
TSQM					X	
Safety Assessments						
Neurologic examination					X	
Abbreviated physical examination					X	An abbreviated physical examination can be performed at any visit after Day 1.
Vital signs	X	X	X	X	X	
ECG					X	
Concomitant medications	Continuous monitoring					
AEs	Continuous monitoring					
Clinical laboratory tests	X		X		X	
Patient safety card review	X	X	X	X	X	
C-SSRS[d]	X		X		X	Perform C-SSRS since last visit assessment.
Pharmacokinetic and Pharmacodynamic Assessments						
Blood samples for PK/free C5		T/P			X	
Blood samples for ADA		T			X	

Table 3: Schedule of Activities: Week 124 to End of Study

Period	Open-Label Extension Period					Notes
Visit[a]	**23**	**24**	**25**	**26**	**27**	Additional visits can be performed as needed. An ED Visit should be performed if patients discontinue early.
Week	**W124**	**W132**	**W140**	**W148/ EOT**	**W156/ EOS/ED in OLE**[b]	
Days and Window	**D869 ± 7**	**D925 ± 7**	**D981 ± 7**	**D1037 ± 7**	**D1093 ± 7**	
Biomarker Research						
Blood samples for biomarkers		T			X	
Blood samples for DNA and RNA					X	Optional; samples collected from patients who consent to DNA and RNA collection. The blood sample for RNA is collected at all time points and the blood sample for DNA is collected on Day 1.[g]
Urine biomarker samples		X			X	
Administration of Study Drug						
Ravulizumab[h]	X	X	X	X		Administer after all other required tests/procedures.

Note: P = postdose; T = trough (predose); X = anytime.

Abbreviations: ADA = antidrug antibody; AE = adverse event; ALSFRS-R = revised amyotrophic lateral sclerosis functional rating scale; C5 = complement component 5; C-SSRS = Columbia-suicide severity rating scale; D = day; ECG = electrocardiogram; ED = early discontinuation; EOS = end of study; EQ-5D-5L = European Quality of Life Health 5-item questionnaire; OLE = Open-Label Extension; PK = pharmacokinetics;; SVC = slow vital capacity; TSQM= Treatment Satisfaction Questionnaire for Medication; W = week; WOCBP = women of childbearing potential

[a] Under reasonable occasional circumstances where a patient is not able to attend a study visit on site, a home visit (where available) or visit at an alternative healthcare facility may be permitted by the Sponsor after discussing with the Alexion Medical Monitor (or delegate). This will be a case-by-case decision (Section 8.1.5).

[b] Patients who discontinue the study during the open-label extension period, the ED in OLE visit should be completed as soon as possible. In addition, a Follow-up Phone Call will be performed 8 weeks (56 days) ± 5 days following the patient's last dose of study drug to collect concomitant medications, nonpharmacological therapies and procedures,VAFS, and AEs.

[c] Ravulizumab dosing is based on the last recorded study visit body weight. When possible, weights should be obtained at every dosing visit; consecutive weights must not be more than 16 weeks apart.

[d] Performed by the Investigator or any designee who has been properly trained and certified for the evaluation, preferably the same Investigator or designee, throughout the study. When possible, ALSFRS-R should be performed first and SVC second.

[e] If a patient is not able to attend the scheduled onsite visit, the ALSFRS-R and EQ-5D-5L can be assessed via a phone call by the Investigator or trained designee.

[f] In addition to SVC in the clinic, home SVC (where regionally available) should be performed using a provided spirometer and under the direction of study staff properly trained for the evaluation (Section 8.2.3). In the event that an SVC measurement cannot be obtained in the clinic due to the COVID-19 pandemic, only home evaluation is required for that visit. Home SVC at screening should be performed after informed consent and after the patient has received training on the spirometer. For subsequent visits, including Day 1, home SVC should be performed within 3 days prior to the scheduled clinic visit.

[g] If Day 1 sample collection is missed, the DNA sample can be collected at any scheduled visit thereafter.

[h] Patients may be allowed to switch from the 10 mg/mL to the 100 mg/mL formulation of ravulizumab with no change to the weight-based dose regimen at or after Week 52 in the Open-Label Extension (OLE) Period (Section 3.1).

2. INTRODUCTION

2.1. Study Rationale

Amyotrophic lateral sclerosis (ALS) is a debilitating neurodegenerative disease characterized by progressive degeneration of upper and lower motor neurons leading to severe disability and eventually death. Currently, riluzole and edaravone are the only available medications approved for the treatment of ALS that may slow disease progression. Management of ALS is otherwise supportive, palliative, and symptom based. Given the seriousness of the disease and limitations of the available treatments, there is a substantial unmet need for developing additional treatments that are efficacious and safe for patients with ALS.

The pathogenesis of ALS is largely unknown, but immune dysregulation and neuroinflammation have been implicated as potential mediators of the disease. The therapeutic rationale for complement component 5 (C5) inhibition in ALS is supported by evidence of dysregulation of the complement system in tissues from patients with ALS. Furthermore, functional and survival benefits of C5 signaling blockade have been demonstrated in animal models of ALS. Ravulizumab (Ultomiris®) is a recombinant, humanized monoclonal antibody (mAb) with high specificity for human C5. Ravulizumab has been shown to achieve immediate, complete, and sustained inhibition of terminal complement in adult patients with paroxysmal nocturnal hemoglobinuria (PNH; approved in the US, EU, and Japan) and in pediatric and adult patients with atypical hemolytic uremic syndrome (aHUS; approved in the US). It is expected that the same dosing regimen will also achieve comparable inhibition of complement-mediated damage in patients with ALS, which may slow ALS disease progression. The primary objective of this study is to investigate the efficacy and safety of ravulizumab in adult patients with ALS.

2.2. Background

2.2.1. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis is a debilitating neurodegenerative disease characterized by progressive degeneration of upper and lower motor neurons leading to severe disability and eventually death. In Europe and North America, the incidence has been estimated as 1-3 per 100,000 (Couratier, 2016; Orsini, 2015). The burden of ALS is substantial with an average life expectancy from symptom onset between 2 and 5 years (Mehta, 2018). Typically, the onset of ALS occurs in the fifth or sixth decade of life and is marked by a progressive loss of motor neurons leading to variable amounts of weakness and spasticity in the limb, bulbar, and respiratory muscles (Swinnen, 2014). Most patients present with limb onset, also referred to as spinal onset, with asymmetric painless weakness in a limb, but in approximately 20% of patients, weakness may be of bulbar onset manifesting as dysarthria or dysphagia. Bulbar onset patients have a poorer prognosis. Patients develop progressive disability limiting ambulation, communication, nourishment, and independence. Declining respiratory function can lead to respiratory insufficiency and failure which often is the cause for death, unless permanent mechanical ventilation is elected (Paulukonis, 2015).

The etiology of ALS is complex. Sporadic ALS, which occurs in individuals who have no apparent family history of the disease, comprises the majority of cases (85% – 90%) whereas familial ALS, with a Mendelian pattern of inheritance occurring in at least 2 people in the same family, accounts for a small fraction of all cases (10% – 15%) (Nowicka, 2019). Gene mutations in ALS have implicated multiple cellular processes in the pathogenesis of ALS, including defects in the regulation of protein homeostasis, RNA homeostasis, and cytoskeletal dynamics (Brown, 2017). Downstream of these proximal events, abnormalities in protein and RNA aggregation, protein degradation, mitochondrial function, endoplasmic reticulum stress, nucleocytoplasmic transport, neuronal excitability, neuronal transport, immune regulation, and neuroinflammation may have negative influences on motor neuron viability in ALS (Beers, 2019; Brown, 2017).

2.2.2. Complement Activation in ALS and Ravulizumab

While the etiology of ALS is largely unknown, neuroinflammation may be a key event in disease pathology (Boillee, 2006; Kjaeldgaard, 2018). Immune dysregulation and neuroinflammation in both the central and peripheral nervous system are common features of familial and sporadic ALS and have negative influences on motor neuron viability in ALS (Beers, 2019). The complement system is a major component of the innate immune system that comprises more than 30 proteins and plays an essential role in pathogen killing, stimulation of phagocytosis, chemoattraction of inflammatory cells, and disposal of self-debris (Chen, 2010). Upregulation of proximal and terminal components of the complement system and its regulators has been identified in the biofluids, neural tissue, and skeletal muscle of patients with ALS and has been corroborated by data from ALS animal models (Parker, 2019). Complement dysregulation likely occurs early in ALS pathogenesis as its deposition has been identified at the neuromuscular junction prior to nerve cell death, making it a potential mediator of the proposed “dying back” effect where motor neuron loss results from axonal damage at the neuromuscular junction (Bahia El Idrissi, 2016; Kjaeldgaard, 2018). Further, quantitative analyses in multiple ALS mouse models show that complement deposition increases over time and correlates with disease progression (Lee, 2017).

Terminal complement, specifically, has been shown to play an important role in the pathology of ALS (Parker, 2019). While plasma levels of proximal complement are similar in ALS patients and normal controls, serum levels of the membrane attack complex, as well as serum and leukocyte levels of C5a, are increased in ALS patients (Mantovani, 2014). Terminal complement is also found to correlate with mediators of neuroinflammation in ALS. Inflammatory M1 macrophages and microglia are associated with disease progression in ALS and these invading cells at the neuromuscular junction express the complement receptor C5aR1 (Lee, 2017; Liao, 2012). Both pharmacologic inhibition and genetic deletion of C5aR1 receptor signaling diminishes recruitment of these inflammatory cells to affected tissue and potentially decreases denervation induced by inflammation (Lee, 2017). Inhibition of terminal complement can alter the course of disease in animal models of ALS. When transgenic hSOD1^{G93A} mice and rats were treated with an inhibitor of C5aR1, both prior to symptom onset and at an early stage of disease, survival was prolonged. Functional benefit as evidenced by a delay in time to significant loss of hind limb strength was also observed. Similar results were observed in animals with a genetic knockout of the C5aR1 receptor, but not when proximal complement components such as C3 were targeted (Lobsiger, 2013; Woodruff, 2014).

The potential for terminal complement inhibition to modify disease progression of ALS is likely dependent on the ability to have a biological effect in the central nervous system (CNS) and neuromuscular junction. Evidence for a potent, selective C5 inhibitor to have biological activity on CNS inflammation is evident with the benefit that has been established for eculizumab (Soliris®) in the treatment of neuromyelitis optica spectrum disorder (NMOSD) (Soliris United States Prescribing Information [USPI]). In NMOSD, an inflammatory disorder of the CNS, treatment with the terminal complement inhibitor eculizumab significantly reduced the risk of relapse (Pittock, 2019). Treatment with eculizumab in NMOSD patients was further shown to produce immediate, complete, and sustained inhibition of serum terminal complement which was shown, in a small cohort of patients, to be mirrored in the cerebrospinal fluid (CSF) (Pittock, 2019; Pittock, 2013). Similarly, evidence for biological activity of selective C5 inhibition at the neuromuscular junction has been demonstrated through the significant treatment effect of eculizumab in generalized myasthenia gravis (gMG) (Soliris USPI). In gMG, a neuroinflammatory disease of the neuromuscular junction, treatment with eculizumab significantly improved patient function in measures of activities of daily living and muscle weakness (Dhillon, 2018). Clinical development programs evaluating the efficacy and safety of ravulizumab for the treatment of patients with gMG and NMOSD are currently ongoing.

Ravulizumab is a novel C5 inhibitor with the potential to alter the disease course of ALS. Ravulizumab has been shown to achieve immediate, complete, and sustained inhibition of terminal complement in patients with PNH and patients with aHUS, for which ravulizumab is approved in the US. The same dosing regimen is expected to achieve comparable inhibition of complement activation in patients with ALS, and it is hypothesized that this inhibition will slow disease progression in these patients through suppression of complement-induced central and peripheral neuroinflammation and associated neuronal death.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

Based on clinical study experience and cumulative clinical study safety data of ravulizumab in PNH and aHUS, ravulizumab has been demonstrated to be well tolerated and safe, and exposure to ravulizumab in humans has not raised any unexpected safety concerns.

Ravulizumab functions by blocking terminal complement; therefore, patients have increased susceptibility to serious infections, in particular *Neisseria meningitidis* (Table 4). Specific risk mitigation measures in place are described in Section 8.1.2.

As with any therapeutic protein, administration of ravulizumab may lead to the development of antidrug antibodies (ADAs). Monitoring of immunogenicity is planned, as described in Section 8.9. Administration of any investigational product may result in infusion reactions. Management of potential infusion reactions is described in Section 10.13.

Table 4: Ravulizumab Identified and Potential Risks

Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Identified risk		
Meningococcal infection	Complement C5 inhibition is known to increase the susceptibility to infections caused by *Neisseria meningitidis*.	Patients must be vaccinated or revaccinated according to current national vaccination guidelines for vaccination use prior to or at the time of initiating dosing with complement inhibitors (eg, eculizumab or ravulizumab).
Potential risks		
Serious infection	This potential risk is based on the mode of action of ravulizumab and experience with the use of eculizumab. Since the relevance of serious infection with ravulizumab therapy has not been confirmed in clinical studies, this remains a potential risk.	Increased awareness of healthcare professionals and patients about the potential risk of serious infection. Monitoring for signs and symptoms of serious infections will be conducted as part of routine safety assessments for this study
Immunogenicity	Treatment with any therapeutic protein has the potential to induce an immune response. Potential clinical consequences may include severe hypersensitivity type reactions, decrease in efficacy and induction of autoimmunity, including antibodies to the endogenous form of the protein (Casadevall, 2002; Li, 2001). Protein therapies administered intravenously have the potential risk of causing local (infusion-site reactions) and systemic reactions (infusion-associated reactions).	In PNH and aHUS patients (N = 333), only 2 (0.60%) treatment-emergent ADA have been reported with ravulizumab. Both were transient in nature and low titer, and no apparent correlation of antibody development to altered pharmacokinetic profile, clinical response, or adverse events was observed
Pregnancy exposure/lactation	No studies of ravulizumab have been conducted in pregnant women. There are no data available on excretion of ravulizumab in breast milk.	Pregnant or nursing female patients are excluded from the clinical study. Patients enrolled in the study, and their spouses/partners, must use a highly effective or acceptable method of contraception for a period of 8 months following the last dose of ravulizumab. Breastfeeding should be discontinued during treatment and up to 8 months after treatment with ravulizumab.

2.3.1.1. Coronavirus Disease 2019

The coronavirus disease 2019 (COVID-19) pandemic is active in many countries at the time of this protocol amendment. Given this unique circumstance, specific consideration has been given to the risks and benefits of the study as they relate to COVID-19, and the global and local changes that exist as a result of the pandemic. This assessment is described in Section 10.14.

2.3.2. Benefit Assessment

Amyotrophic lateral sclerosis is a devastating neurodegenerative disease with a poor prognosis, rapid progression, and limited treatment options for which discovery of new therapies is important to address unmet medical need. Clinical research provides the best modality to identify effective treatments with the potential to slow disease progression and improve survival which are of critical importance to patients with ALS and their providers. Although the efficacy of ravulizumab has not been previously studied in patients with ALS, it represents an appropriate candidate for investigation due to its plausible mechanism of action in ALS and reliable pharmacokinetic (PK) and pharmacodynamic (PD) properties as well as the demonstrable functional benefit of complement inhibition in ALS animal models and in the treatment of other neuroinflammatory conditions. The scientific and therapeutic hypothesis for the potential benefit in ALS is discussed in Section 2.2.2.

2.3.3. Overall Benefit:Risk Conclusion

Given the severity of ALS, collective consideration of the unmet medical need and plausible mechanism of action with the expected safety profile and mitigation measures in place provides support for initiation of a Phase 3 clinical study with ravulizumab.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of ravulizumab is provided in the Investigator's Brochure.

3. STUDY DESIGN

3.1. Overall Design

Study ALXN1210-ALS-308 is a Phase 3, double-blind, randomized, placebo-controlled, parallel group, multicenter study to evaluate the efficacy and safety of ravulizumab in adult patients with ALS. There are 3 periods in this study: Screening Period, Randomized Controlled Period, and Open-Label Extension Period.

Patients will be screened for eligibility for up to 4 weeks during the Screening Period. Approximately 354 eligible adult patients with ALS from North America, Europe, and the Asia-Pacific region will be enrolled into the study. Patients who are not taking or who are on a stable regimen of riluzole and/or edaravone at Screening will be considered for participation. Eligible patients will be randomized in a 2:1 ratio to receive weight-based intravenous (IV) infusion of ravulizumab or matching placebo until Week 50 during the double-blind Randomized Controlled Period. Randomization will be stratified based on the site of ALS muscle weakness onset (bulbar vs other) and background ALS treatment (riluzole and/or edaravone vs neither ALS therapy) (Section 9.2.1; Table 7). For each patient, the Randomized Controlled Period ends and the Open-Label Extension Period starts when the patient has completed the Week 50 visit assessments. Regardless of prior treatment allocation, all patients will receive ravulizumab treatment during the Open-Label Extension Period. The Open-Label Extension Period will continue for up to 2 years, or until ravulizumab is approved and/or available (in accordance with country-specific regulations), whichever occurs first. Patients may be allowed to switch from the 10 mg/mL to the 100 mg/mL formulation of ravulizumab with no change to the weight-based dose regimen at or after Week 52 in the OLE Period. After the end of treatment visit or early discontinuation, patients will be followed for an additional 8 weeks after the last dose of study drug. Treatment allocation will be blinded to patients, study sites, and Alexion throughout the Randomized Controlled Period and will remain blinded to patients and study sites until end of the study.

One interim analysis is planned during the Randomized Controlled Period (Section 9.5). An independent data monitoring committee (IDMC) will be established to conduct the unblinded interim analysis and periodic review of accumulating data for patient safety and efficacy during the study. The interim analysis for futility will be conducted when approximately 33% of patients have completed the Week 26 (6 months) visit. The study may be stopped if considered futile.

3.2. Scientific Rationale for Study Design

3.2.1. Study Population and Treatment Duration

Neuroinflammation and complement dysregulation are hypothesized to be common pathways in both sporadic and familial ALS. Complement dysregulation may be important to disease progression both early and throughout the course of disease, and thus a broad study population is targeted. The eligible study population fulfills the El Escorial diagnostic criteria of possible, probable, probable laboratory supported, or definite ALS, is within 36 months or less from disease onset, and demonstrates a slow vital capacity (SVC) of 65% predicted or more and not yet requiring respiratory support. Given that the typical time from onset of muscle weakness to

diagnosis is approximately 1 year, these characteristics will likely permit enrollment of patients in the early to mid-stages with mild to moderate manifestations of the disease. Given the heterogenous nature of ALS, including rates of disease progression across patients, a minimal prestudy progression criteria of 0.3 points per month or worse on the amyotrophic lateral sclerosis functional rating scale-revised (ALSFRS-R), calculated as (48 – ALSFRS-R at Screening)/(months from onset to Screening) will be used to enrich for patients more likely to demonstrate disease progression in the course of the study. The selected population is hypothesized to better allow for the potential detection of a treatment benefit.

A randomized, double-blind, placebo-controlled study design is selected to provide the most robust evidence of the effectiveness of the intervention on disease progression and safety. Randomization minimizes the effects of baseline differences and confounding factors on the study population. The use of a placebo comparator allows for the true treatment effect of the intervention to be established while also allowing for study management, drug administration, and assessments to be conducted similarly between treatment groups, thus minimizing the potential for bias. An unequal randomization scheme was chosen to decrease the number of patients receiving placebo. Patients may continue to receive standard of care treatment for ALS, which may include riluzole and/or edaravone as detailed in the inclusion/exclusion criteria. To reduce the heterogeneity in the study results, a stratification scheme has been implemented. This stratification includes the use of background therapies which are permitted, but not mandated, in accordance with ethical standards.

A 50-week primary evaluation period was selected to ensure characterization of effects on multiple functional and survival endpoints. This timeframe allows for a rigorous assessment of ALSFRS-R in which potential differences can both be detected and characterized for magnitude and durability of response. The 50-week treatment period also allows the opportunity to characterize potential treatment effects on other important endpoints, such as survival, which may take longer to demonstrate than the ALSFRS-R.

A study design with an interim analysis was chosen to allow consideration for early stopping in the case of futility, which would minimize the duration of exposure to an ineffective therapy.

An OLE Period was chosen to ensure that all patients participating in this study have the opportunity to receive active treatment after the completion of the Randomized Controlled Period of the study. This period also allows for further evaluation of longer term safety and efficacy of the study intervention.

In this study patients may be allowed to switch from the 10 mg/mL to the 100 mg/mL formulation of ravulizumab with no change to the weight-based dose regimen during the OLE Period. The 100 mg/mL IV formulation of ULTOMIRIS® (ravulizumab) was approved in 2020 by the FDA and the European Commission for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS). The 100 mg/mL ravulizumab is a higher concentration IV formulation which provides shorter preparation and infusion times while delivering comparable PK, safety and efficacy to the 10 mg/mL formulation of ravulizumab. Clinical data from Study ALXN1210-PNH-201 and Study ALXN1210-PNH-302 shows no change in the benefit/risk profile of ravulizumab following administration of the approved weight-based doses of ravulizumab using the 100 mg/mL formulation in patients with PNH.

3.2.2. Rationale for Primary Endpoint: ALSFRS-R

The ALSFRS-R is a validated instrument and the most widely used instrument to measure physical function in performance of daily living activities across the 4 domains of gross motor activity, fine motor activity, bulbar, and respiratory function in patients with ALS (Cedarbaum, 1999; Section 8.2.1). The scale is composed of 12 items with a maximum score of 48, with lower scores associated with declining function. Changes in ALSFRS-R total score have been shown to be reproducible over time and to correlate with survival and other functional measures. It is considered an important efficacy endpoint in clinical studies and clinical practices (Castrillo-Viguera, 2010).

3.2.3. Rationale for Secondary Endpoints Included in the Multiplicity Adjustment

3.2.3.1. Ventilation Assistance-Free Survival (VAFS)

Survival is accepted as a clinically relevant outcome measure in ALS clinical studies. However, overall survival in ALS can be significantly influenced by the use of noninvasive ventilation (NIV) or permanent assisted ventilation (PAV) which can prolong overall survival without altering the underlying disease pathology. To account for the prolongation of survival in the absence of disease modification, ventilation assistance-free survival (VAFS), a composite endpoint accounting for survival and severe respiratory failure, is defined. In the absence of uniform guidelines for the initiation of NIV and PAV, this endpoint is defined around dependence based on the continuous or nearly continuous need for ventilation assistance. Therefore, VAFS is defined for this study as the time to the earliest occurrence of one of the following events: all-cause mortality; first use of NIV for ≥ 22 hours per day for ≥ 10 consecutive days; or first use of PAV for ≥ 22 hours per day for ≥ 7 consecutive days.

3.2.3.2. Slow Vital Capacity (SVC)

Slow vital capacity is defined as the amount of air expelled from the lungs during a slow, gentle breath, which has been shown to correlate with clinical events such as use of assisted ventilation, tracheostomy, and ultimately, death. Patients with slower decline in SVC could breathe unassisted and survive longer than patients whose SVC declined faster (Andrews, 2018).

Compared with forced vital capacity (FVC), SVC may be easier to measure in ALS patients as patients with loss of muscle function in the face and mouth are still able to perform the gentler test and it is less subject to the fatigue and bronchospasm that can underestimate lung capacity measured by FVC.

Slow vital capacity is considered as a prognostic marker in the clinic and may predict disease progression, respiratory functional decline, and survival.

3.3. Justification for Dose

The dosing regimen of ravulizumab was designed to target immediate, complete, and sustained inhibition of terminal complement in patients. The weight-based doses of ravulizumab in the PNH program were based on PK/PD data from early and late clinical development studies in healthy adult volunteers and patients with PNH. The proposed ravulizumab dosage regimen is the approved regimen for the treatment of patients with PNH and aHUS in the Ultomiris USPI, the European Commission in the EU and the Pharmaceuticals and Medical Devices Agency in

Japan. In ALS patients and preclinical models, dysregulation of the complement system has been identified prior to the onset of neurodegeneration. Inhibition of terminal complement may therefore diminish neuroinflammatory damage in ALS. Based on this and the PK, PD, ADA, efficacy, and safety data generated in the ravulizumab development program, the body weight-based dosage regimen for treating adult patients with PNH and aHUS has been selected for this study, and is expected to be beneficial in treating patients with ALS through immediate, complete and sustained inhibition of terminal complement activation.

3.4. End of Study Definition

A patient is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities (SoA; Section 1.3).

The end of the study is defined as the date the last patient completes the last visit shown in the SoA.

4. OBJECTIVES AND ENDPOINTS

Objective	Endpoints
Primary	
To evaluate the effect of ravulizumab compared with placebo on amyotrophic lateral sclerosis functional rating scale-revised (ALSFRS-R) score in adult patients with amyotrophic lateral sclerosis (ALS)	Change from baseline in ALSFRS-R total score at Week 50
Secondary	
To evaluate the effect of ravulizumab compared with placebo on ventilation assistance-free survival (VAFS) in adult patients with ALS	Time to the earliest occurrence of 1 of the following events during the 50-week Randomized Controlled Period: • All-cause mortality • First use of non-invasive ventilation (NIV) for ≥ 22 hours per day for ≥ 10 consecutive days • First use of permanent assisted ventilation (PAV) for ≥ 22 hours per day for ≥ 7 consecutive days
To evaluate the effect of ravulizumab compared with placebo on respiratory function in adult patients with ALS	Change from baseline in percent (%) predicted slow vital capacity (SVC) at Week 50
To evaluate the safety of ravulizumab compared with placebo in adult patients with ALS	Incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and TEAEs leading to study drug discontinuation
To evaluate the effect of ravulizumab compared with placebo on muscle strength in adult patients with ALS	Percent change in combined muscle megascore from baseline at Week 50 as assessed by handheld dynamometry (HHD)
To evaluate the effect of ravulizumab compared with placebo on neurofilament light chain (NfL) concentration in adult patients with ALS	NfL concentration in serum at Week 50
To characterize the pharmacokinetics (PK) of ravulizumab in adult patients with ALS	Change in serum ravulizumab concentration over the study duration
To characterize the pharmacodynamics (PD) of ravulizumab in adult patients with ALS	Change in serum free complement component 5 (C5) concentration over the study duration
To characterize the immunogenicity of ravulizumab in adult patients with ALS	Presence and titer of antidrug antibodies (ADAs)
Exploratory	
To evaluate the effect of ravulizumab compared with placebo on respiratory function in adult patients with ALS	Time to first instance of SVC < 50% predicted during the 50-week Randomized Controlled Period
To evaluate the effect of ravulizumab compared with placebo on overall health-related quality of life in adult patients with ALS	• Change from baseline in Short Form Health Survey (SF-36) at Week 50 • Change from baseline in European Quality of Life Health 5-item questionnaire (EQ-5D-5L) at Week 50
To evaluate the safety of ravulizumab compared with placebo in adult patients with ALS	• Shifts from baseline in Columbia-suicide severity rating scale (C-SSRS) at Week 50 • Change from baseline in vital signs, electrocardiogram (ECG) parameters, and clinical laboratory assessments
To characterize biomarkers in adult patients with ALS	Change from baseline in levels of biomarkers of complement dysregulation, neuroinflammation and neurodegeneration

Objective	Endpoints
To evaluate the effect of ravulizumab compared with placebo on ALS-related health quality of life in adult patients with ALS	Change from baseline in ALS assessment questionnaire (ALSAQ-40) score at Week 50
To characterize the effect of ravulizumab compared to placebo on disease stage in adult patients with ALS	Any increase from baseline stage on the King's staging system at Week 50
To evaluate the long-term efficacy of ravulizumab in adult patients with ALS	Change in ALSFRS-R total score, VAFS, SVC, HHD, and patient-reported outcome measures over time in all patients exposed to ravulizumab during the Open-Label Extension Period
To evaluate the long-term safety of ravulizumab in adult patients with ALS	Incidence of TEAEs, TESAEs, and TEAEs leading to study drug discontinuation during the Open-Label Extension Period

5. STUDY POPULATION

Prospective approvals of protocol deviations to enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

Age

1. 18 years of age or older, at the time of signing the informed consent.

Type of Patient and Disease Characteristics

2. A diagnosis of ALS, defined as meeting the possible, laboratory-supported probable, probable, or definite criteria for a diagnosis of ALS according to the revised World Federation of Neurology El Escorial criteria. Patients diagnosed with either sporadic or familial ALS are eligible for enrollment.
3. ALS onset, defined as time of onset of first muscle weakness (eg, limb weakness, dysarthria, dysphagia, shortness of breath), ≤ 36 months from the Screening Visit.
4. Prestudy ALSFRS-R progression between disease onset and screening of -0.3 points per month or worse (calculated by ALSFRS-R total score decline from 48 divided by the months since onset of ALS symptoms).
5. Upright SVC ≥ 65% predicted at Screening.
6. Vaccinated against *N. meningitidis* within 3 years prior to, or at the time of, initiating ravulizumab. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive appropriate prophylactic antibiotics until 2 weeks after the vaccination.
7. Patients who enter the study receiving standard of care for ALS (ie, riluzole and/or edaravone), either in combination or monotherapy, must be on a stable dosing regimen of adequate duration prior to screening with no plan to discontinue or to change the dose during the study period as follows:
    - If a patient who enters the study is receiving riluzole, the patient must have been on a stable dose of riluzole for ≥ 30 days prior to Day 1.
    - If a patient who enters the study is receiving edaravone, the patient must have initiated edaravone ≥ 60 days (2 treatment cycles) prior to Day 1.

Note: Patients who are naïve to ALS therapies or have not taken approved ALS therapies for at least 30 days before screening are allowed to enroll.

Weight

8. Body weight ≥ 40 kg at Screening.

Sex

9. Male and/or female

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

- Male patients:

a. Male patients must agree to use contraception as detailed in the protocol (Section 10.4) during the treatment period and for at least 8 months after the last dose of study drug and refrain from donating sperm during this period.

- Female patients:
  - A female patient is eligible to participate if she is not pregnant, not breastfeeding, and meets at least one of the following conditions:
  - Not a woman of childbearing potential (WOCBP) (Section 10.4.1)
    - OR
  - Is a WOCBP and using a highly effective or acceptable contraceptive method as described in Section 10.4 during the treatment period and for a minimum of 8 months after the last dose of study drug.

The Investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study drug. A WOCBP must have a negative pregnancy test at Screening and before the first dose of study drug. Additional requirements for pregnancy testing during and after study drug are described in Section 10.4. The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

10. Capable of giving written or verbal informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

5.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Medical Conditions

1. History of *N. meningitidis* infection.
2. Human immunodeficiency virus (HIV) infection (evidenced by HIV-1 or HIV-2 antibody titer).
3. History of unexplained infections.
4. Active systemic bacterial, viral, or fungal infection within 14 days prior to study drug administration on Day 1.
5. Presence of fever ≥ 38°C (100.4°F) within 7 days prior to study drug administration on Day 1.
6. Hypersensitivity to murine proteins or to 1 of the excipients of ravulizumab.

7. Dependence on invasive or non-invasive mechanical ventilation. Dependence on mechanical ventilation is defined as being unable to lie flat (supine) without it, unable to sleep without it, or daytime use > 6 hours per day for > 3 days per week. Non-invasive ventilation for sleep apnea is allowed subject to discussion with Medical Monitor.
8. Any medical condition that, in the opinion of the Investigator, might interfere with the patient's participation in the study, poses any added risk for the patient, or confounds the assessment of the patient.
9. The presence of unstable psychiatric disease or dementia that might interfere with the patient's participation in the study, poses any added risk for the patient, or confounds the assessment of the patient.
10. History of drug and/or alcohol abuse (according to Diagnostic and Statistical Manual of Mental Disorders) within 1 year of screening that would limit patient participation in the study as determined by the Investigator.
11. History of Parkinson's disease, myasthenia gravis, multiple sclerosis, or any other neurological disorder that may confound the diagnosis or assessment of the patient as determined by the Investigator.

Prior/Concomitant Therapy

12. Previously or currently treated with a complement inhibitor.
13. Use of IV immunoglobulin (IVIg) within 3 weeks prior to screening.
14. Has a diaphragm pacing system (DPS) at study entry or anticipate DPS placement during the course of the study.

Prior/Concurrent Clinical Study Experience

15. Participation in any other investigational product study or exposure to an investigational drug or device within 30 days of screening or 5 half-lives of the study drug, whichever is greater or any prior exposure to gene therapy.
16. Receipt of stem cell transplant therapy as an investigational treatment for ALS < 90 days from the date of last transplant.

Other Exclusions

17. Pregnant, breastfeeding, or intending to conceive during the course of the study.

5.3. Lifestyle Considerations

There is no lifestyle restriction for this study.

5.4. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomly assigned to study drug. A minimal set of screen failure information is required to ensure transparent reporting of screen failures to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (eg, failed

eligibility criteria), and any adverse events (AEs), including any serious adverse events (SAEs) and any related concomitant medication, occurring during the screening period.

Individuals who do not meet the criteria for participation in this study (screen failure) due to a reason that is expected to resolve or has resolved may be rescreened based on discussion and agreement between the Investigator and the Medical Monitor.

6. STUDY DRUG

Study drug is defined as any investigational drug(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Drug(s) Administered

In this study, patients will be randomized 2:1 to receive blinded ravulizumab or placebo treatment during the Randomized Controlled Period; during the Open-Label Extension period, all patients will receive open-label ravulizumab treatment (Table 5; Figure 1).

Refer to Section 8.1.4 for study drug dosage and administration and Section 1.3 SoA for dosing schedules. Detailed description of the study drug is provided in the Pharmacy Manual.

Table 5: Study Drugs

Study drug name	Ravulizumab	Placebo
Dose formulation	Vial	Vial
Physical description	Liquid solution practically free from particles	Liquid solution practically free from particles
Unit dose strength(s)	300 mg (10 mg/mL concentrated solution or 100 mg/mL formulation)	Placebo
Dosage level(s)[a]	Weight-based dosing; starting 2 weeks after the initial loading dose, maintenance dose q8w	Weight-based dosing; starting 2 weeks after the initial loading dose, maintenance dose q8w
Route of administration	IV infusion	IV infusion
Use	Experimental	Placebo comparator
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by Alexion or contracted manufacturing organization	Provided centrally by Alexion or contracted manufacturing organization
Packaging and labeling	Ravulizumab will be provided in glass vials and stoppered with a butyl rubber stopper with an aluminum overseal and a flip-off cap. Study drug will be supplied in kits and labeled as required per country requirement.	Placebo will be provided in glass vials and stoppered with a butyl rubber stopper with an aluminum overseal and a flip-off cap. Placebo will be supplied in kits and labeled as required per country requirement.

[a] Detailed information of study drug dose administration is provided in Section 8.1.4.
Abbreviations: IMP = investigational medicinal product; IV = intravenous; NIMP = non-investigational medicinal product; q8w = every 8 weeks

6.2. Preparation/Handling/Storage/Accountability

Upon arrival of the study drug at the study site, the study drug kits should be removed from the shipping container and stored in their original cartons under refrigerated conditions at 2°C to 8°C (35°F to 47°F) and protected from light. Study drugs should not be frozen.

Study drugs must be stored in a secure, limited-access storage area with temperature monitored daily.

Infusions of study drug should be prepared using aseptic technique. Ravulizumab and placebo will be further diluted in a 1:1 ratio with compatible diluent. Ravulizumab and placebo will be filtered with a 0.2 micron filter during infusion.

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.
- Only patients enrolled in the study may receive the study drug and only authorized site staff may supply or administer the study drug. All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study drugs are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization

Patients will be randomly allocated on Day 1 to one of two treatment groups after the Investigator and Medical Monitor have verified that they are eligible. Patients will be stratified by site of muscle weakness onset (bulbar vs other) and background ALS treatment (riluzole and/or edaravone vs neither ALS therapy) (Section 9.2.1) and randomized 2:1 either to ravulizumab IV infusion or placebo IV infusion. Patients will be centrally randomized using Interactive Response Technology (IRT).

6.3.2. Blinding

Patients, all investigative site personnel and any Sponsor employee or delegate directly associated with the conduct of the study will be blinded to patient treatment assignments. The blinding will be maintained by using identical study drug kits and labels for ravulizumab and placebo. The placebo will have an identical appearance to that of ravulizumab. The randomization code will be maintained by the IRT provider. Patients who elect to continue treatment after completion of the Randomized Controlled Period enter the Open-Label Extension Period at the end of the Week 50 visit after completing all scheduled assessments and before

receiving ravulizumab. To maintain blinding to the patient's treatment assignment during the Randomized Controlled Period, patients in the placebo group will receive a blinded loading dose of ravulizumab, and patients in the ravulizumab group will receive a blinded ravulizumab dose of 900 mg. Starting at Week 52, all patients will begin open-label ravulizumab maintenance doses every 8 weeks (q8w). For patients in the ravulizumab group, a blinded ravulizumab dose of 900 mg was chosen to ensure maintenance of complete C5 inhibition until the next scheduled maintenance dose at Week 52. Investigators are to avoid any unscheduled clinical laboratory tests which could potentially unblind study patients (eg, complement activity via assays such as CH50). Blind to prior assignment will be maintained for patients and providers (study site) during the Open-Label Extension Period.

In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a patient's intervention assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a patient's intervention assignment unless this could delay emergency treatment of the patient. The Investigator will be able to unblind the patient's treatment allocation using the IRT. If a patient's intervention assignment is unblinded, Alexion must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation, as applicable.

When unblinding is the result of an AE which is unexpected or related and serious, the blind will be broken for that specific patient only. The blind with regard to treatment allocation for that specific patient will be maintained for all persons responsible for the ongoing conduct of the study (such as the management, monitors, Investigators, etc) and those responsible for data analysis and interpretation of results at the conclusion of the study, such as biometrics personnel.

Unblinded information will only be accessible to those who need to be involved in the safety reporting to Health Authorities, Independent Ethics Committees (IECs), Institutional Review Boards (IRBs), and/or IDMC.

Any patient who is unblinded during the Randomized Controlled Period will be discontinued from the study.

6.4. Study Drug Compliance

The infusion of study drug into patients will be under the supervision of the Investigator or their designee to ensure that patients receive the appropriate dose at the appropriate time points during the study.

The date and time of each dose administered will be recorded in the source documents and CRF.

6.5. Concomitant Therapy

6.5.1. Allowed Medications and Therapies

6.5.1.1. Palliative and Supportive Care

Palliative and supportive care is permitted during the course of the study for underlying conditions.

6.5.1.2. ALS-Specific Therapies

There are 2 therapies currently available for treating ALS that may slow disease progression: riluzole and edaravone.

- Patients who are naïve to ALS therapies or have not taken ALS therapies for at least 30 days before screening are allowed to enroll.
- For a patient who is on one or more ALS-specific therapies at Day 1 of the study, the patient must be on a stable dose regimen of riluzole for at least 30 days and/or on a stable treatment of edaravone for at least 60 days (2 treatment cycles) prior to Day 1 and has no plan to discontinue or change dose during the study.
  - Temporary discontinuations or dose modifications of riluzole or edaravone are acceptable at the discretion of the Investigator for medical reasons.
  - Patients receiving edaravone should not receive edaravone infusions on days when study drug is to be administered.
- Patients who do not enter the study on riluzole and/or edaravone will not be permitted to start treatment with either drug during the Randomized Controlled Period. Initiation of riluzole and/or edaravone is permitted during the Open-Label Extension Period.

6.5.1.3. Other Allowed Therapies

- Vitamin B12, vitamin E, creatine, coenzyme Q10, biotin supplements, and l-serine are permitted in this study. Patients who take any or all of these supplements should be on a stable dose beginning 14 days prior to first dose of study drug and remain on a stable dose for the duration of the Randomized Controlled Period of the study unless alteration in dose is deemed medically necessary or reviewed with the Medical Monitor.
- All other vitamins and supplements are permitted on this study. Patients are encouraged to remain on stable dosing for the duration of the Randomized Controlled Period of the study.
- Patients who received stem cell transplant therapy as an investigational treatment for ALS are permitted to enroll in the study after a minimum washout period of 90 days from date of last transplant.

6.5.2. Disallowed Medications and Therapies

The following medications and therapies are prohibited during the study:

- Chronic treatment with IVIg for ALS disease management during the study is prohibited, **Note**: If IVIg is deemed necessary for treatment of an acute condition for which IVIg is an indicated therapy, acute treatment with IVIg may be considered on a case by case basis in consultation with the Medical Monitor.
- Chronic use of plasmapheresis/plasma exchange (PP/PE) is prohibited during the study. However, if it is deemed necessary by the Investigator for treatment of an acute condition for which PP/PE is indicated, acute treatment of PP/PE may be considered on a case by case basis in consultation with the Medical Monitor. No more than 1 treatment cycle of PP/PE will be allowed.

- Eculizumab or other complement inhibitory agent is prohibited.
- Chronic systemic use of immunosuppressive therapies, defined as using any systemic immunosuppressive agent for ≥ 14 days, is prohibited during the study.

  Note: Topical and inhaled immunosuppressive agents are permitted.

  Note: Use of systemic corticosteroids for ≥ 14 days may be considered on a case-by-case basis in consultation with the Medical Monitor
- Rituximab and other biologic or immunomodulatory therapies are prohibited during the study.
- Tauroursodeoxycholic acid (TUDCA) and sodium phenylbutyrate in combination or as individual therapies are prohibited during the study.
- Any off-label usage of an approved product currently under investigational use for the treatment of ALS during the study is prohibited.

6.6. Dose Modification

Dose modification is not permitted for this study. However, in the event of a missed or incomplete dose, and with the guidance of the Sponsor, supplemental dosing may be employed in order to maintain therapeutic steady state concentrations from disruptions in scheduled study drug dosing.

6.7. Intervention after the End of the Study

Ravulizumab will not be provided to the patients after the last scheduled dosing (Section 1.3). After the end of therapy visit or ED, all patients will be followed for an additional 8 weeks after the last dose of study drug.

7. DISCONTINUATION OF STUDY DRUG AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Drug

In rare instances, it may be necessary for a patient to permanently discontinue study drug. If study drug is permanently discontinued, the patient should complete the ED visit (Section 1.3) for safety follow-up before discontinuing from the study. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study drug and follow-up and for any further evaluations that need to be completed.

Patients should be considered for discontinuation from study drug if any of the following occur during the study:

- Serious hypersensitivity reaction;
- Severe uncontrolled infection;
- Use of disallowed medication as defined in Section 6.5.2;
- Pregnancy or planned pregnancy; or
- Sponsor or the Investigator deems it is in the best interest of the patient.

7.2. Patient Discontinuation/Withdrawal from the Study

- All efforts should be made to ensure patients are willing to comply with study participation prior to conducting the screening procedures. The study staff should notify Alexion and their site monitor of all study withdrawals as soon as possible. The reason for patient discontinuation must be recorded in the source documents and electronic CRF (eCRF).
- A patient may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral compliance, or administrative reasons.
- At the time of discontinuing from the study, if possible, an ED visit corresponding with the period of the study the patient is in should be conducted. The ED visit should be conducted as soon as possible, and no later than 8 weeks after the last dose of study drug, as shown in the SoA (Section 1.3). A follow-up phone call will be performed at 8 weeks (56 days) ± 5 days following the patient's last dose of study drug to collect concomitant medications, non-pharmacologic therapies, VAFS, procedures, and AEs.
    - The patient will be permanently discontinued both from the study drug and from the study at that time.
- If the patient withdraws consent for disclosure of future information, Alexion may retain and continue to use any data collected before such a withdrawal of consent.
- If a patient withdraws from the study, the patient may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records as well as inform the site monitor and Sponsor.

7.3. Lost to Follow-up

If a patient fails to return, or is otherwise unavailable, for a scheduled visit within the acceptable visit window (Section 1.3), the site study staff must make a reasonable attempt to contact the patient to determine the reason for missing the appointment. As it is vital to obtain any patient's missing visit information to ensure the missed appointment was not due to an AE, every effort must be made to undertake protocol-specified safety follow-up procedures.

In the exceptional circumstance where a patient cannot or does not come to the study site for examination, the patient will be instructed to see his or her local neurologist or physician. In this event, if possible, the Investigator or designee will contact the local neurologist or physician to obtain as much information as possible about the patient's medical and neurological condition, and provide clinical guidance, if needed. The study site will obtain relevant medical records as documentation from the local physician's examination and enter relevant data in the eCRF as appropriate.

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered as lost to follow-up.

Discontinuation of specific sites or of the study as a whole are described in Section 10.1.8.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with Alexion immediately upon occurrence or awareness to determine if the patient should receive study drug.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1. General Assessments

8.1.1. Medical History and ALS History and Diagnosis

The Principal Investigator or Sub-Investigator will review the patient's medical history including ALS history and diagnosis.

The following will be evaluated and documented at the Screening Visit and/or other visits as specified in the SoA (Section 1.3):

- Time of ALS onset (defined as time of onset of first muscle weakness symptom date).
- Date of ALS diagnosis.
- Criteria for ALS diagnosis, defined as meeting the clinically possible, laboratory-supported probable, probable, or definite criteria for a diagnosis of ALS according to the revised World Federation of Neurology El Escorial criteria (Brooks, 2000) (Section 10.5).
- ALS stage will be evaluated using King's staging system (KSS) (Balendra, 2019) by the Investigator or trained designee. Stage will be assigned based on the number of involved CNS regions and nutritional and respiratory status.

8.1.2. Vaccine and Antibiotic Prophylaxis

As with any terminal complement antagonist, the use of ravulizumab increases the patient's susceptibility to meningococcal infection (*N. meningitidis*). To reduce the risk of meningococcal infection, all patients must be vaccinated against meningococcal infections within the 3 years before or at the time of initiating study drug.

- Patients who initiate study drug less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics from the first day of study drug treatment until 2 weeks after vaccination.
- Patients must be vaccinated or revaccinated according to current national vaccination guidelines or local practice for vaccination use with complement inhibitors (eg, eculizumab, ravulizumab).
- Vaccines against serotypes A, C, Y, W135, and B, where available, are recommended to prevent common pathogenic meningococcal serotypes.
- Vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given according to official guidance and local practice on the appropriate use of antibacterial agents.
- All patients should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics, if necessary.
- It is recommended that sites also follow relevant national vaccination guidelines and local practice for patients with ALS (eg, pneumococcal and influenza [flu] vaccination).

8.1.3. Inclusion/Exclusion Criteria

All inclusion (Section 5.1) and exclusion (Section 5.2) criteria must be reviewed by the Investigator or qualified designee to ensure the patient qualifies for study participation.

Both the Investigator and Alexion must approve patient eligibility before enrollment.

8.1.4. Study Drug Administration

This section describes the dosage regimen of study drugs. At the scheduled dosing visits (Section 1.3), study drug infusion should be performed after all other tests and procedures have been completed, excluding the postdose blood sampling for PK and free C5.

Refer to Section 6 for additional information on study drugs including preparation, handling, storage, and accountability. For detailed instructions, refer to the Pharmacy Manual.

The ravulizumab dose for each patient will be based on last recorded body weight. The dosing regimen (Table 6) consists of a loading dose followed by maintenance dosing administered q8w. The maintenance dose should be initiated 2 weeks after the loading dose administration.

Table 6: Weight-based Doses of Ravulizumab

	Body Weight (kg)[a, b]	Dose (mg)
Loading dose	≥ 40 to < 60	2400
	≥ 60 to < 100	2700
	≥ 100	3000
Maintenance dose	≥ 40 to < 60	3000
	≥ 60 to < 100	3300
	≥ 100	3600

[a] Dose regimen will be based on the last recorded study visit body weight.
[b] In the event that a patient drops below 40 kg during the course of the study the approved ravulizumab aHUS dosing for patients weighing 30 - 40 kg will be used: a loading dose of 1200 mg and maintenance dose of 2700 mg, and in the event that a patient drops below 30 kg during the course of the study the approved ravulizumab aHUS dosing for patients weighing 20 - 30 kg will be used: a loading dose of 900 mg and maintenance dose of 2100 mg.
Abbreviation: aHUS = atypical hemolytic uremic syndrome

For each patient, the entire treatment duration is up to 156 weeks, consisting of a Randomized Controlled Period (50 weeks) and an Open-Label Extension Period (up to 106 weeks). Study drug administration will end when all patients have completed the 2-year Open-Label Extension Period, or ravulizumab is approved and/or available (in accordance with country-specific regulations), or anytime during the Open-Label Extension Period at the discretion of Alexion, whichever occurs first.

8.1.4.1. Randomized Controlled Period

The Randomized Controlled Period is a double-blind, randomized, placebo-controlled period. Eligible patients will be randomized 2:1 to receive blinded doses of ravulizumab or placebo during the Randomized Controlled Period (Day 1 through Week 42).

- Patients in the ravulizumab group will receive a blinded loading dose of ravulizumab on Day 1, followed by a blinded maintenance dose on at Week 2 (Table 6), then once q8w up to Week 42 (inclusive) (Table 6).
- Patients in the placebo group will receive a blinded matching placebo dose via IV infusion on Day 1, followed by a blinded matching placebo maintenance dose at Week 2, then q8w up to Week 42 (inclusive).

8.1.4.2. Open-Label Extension Period

Patients who elect to continue treatment after completion of the Randomized Controlled Period enter the Open-Label Extension Period at the completion of all scheduled predose assessments for the Week 50 visit and before receiving ravulizumab.

- Patients in the placebo group may switch to receive a blinded loading dose of ravulizumab at Week 50 (Table 6).
- To ensure treatment allocation remains blinded to patients, Investigators, and site staff, as well as Sponsor staff or delegates, patients in the ravulizumab group will receive a blinded ravulizumab dose of 900 mg at Week 50. The 900 mg dose at Week

50 is chosen to ensure maintenance of complete C5 inhibition until the next scheduled maintenance dose.

Starting at Week 52, all patients will receive open-label ravulizumab maintenance doses q8w (Table 6) until the end of the Open-Label Extension Period when all patients have completed 2 years of ravulizumab or ravulizumab is approved and/or available (in accordance with country-specific regulations). Patients may be allowed to switch from the 10 mg/mL to the 100 mg/mL formulation of ravulizumab with no change to the weight-based dose regimen at or after Week 52 in the OLE Period.

8.1.5. Visits at Home or Alternative Healthcare Facilities

If available, patients may have an opportunity to receive study drug administration remotely at a medical facility that is located near the patient's home or at the patient's home with the permission of the Investigator, after discussion with the Alexion medical monitor (or delegate), in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities. Home infusions may be considered only for patients who have tolerated previous drug infusions well, without clinically significant infusion reactions, at the study site.

Remote visit options may be at the Investigator's discretion and oversight, in accordance with the local regulations, and conducted by a qualified medical professional. Information about AEs, concomitant medications, and ALS signs or symptomatology must be sent to the Investigator's site for evaluation on the day of the remote visit. In case of any signs or symptoms indicating an SAE, the patient may need to be evaluated at the study site or in an emergency room setting.

Monitoring, treatment, and management of infusion reactions for patients receiving drug infusions at home are described in Section 10.13.

8.2. Efficacy Assessments

8.2.1. Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R)

The ALSFRS-Revised (Cedarbaum, 1999) is a validated instrument for evaluating the levels of the functional status of patients with ALS in 4 areas, including bulbar, gross motor activity, fine motor activity, and respiratory functions. The scale includes 12 functional items and each item is rated on a 0 to 4 scale, with a maximum total score of 48 (Section 10.6). A higher score indicates greater retention of function.

In this study, the ALSFRS-R will be performed throughout the study by the Investigator or any designee who has been properly trained for the evaluation. When possible, it is highly recommended that all assessments be performed by the same assessor.

The ALSFRS-R will be assessed as indicated in the SoA (Section 1.3). At the time points specified in the SoA, or if a patient is not able to attend the scheduled onsite visit, the ALSFRS-R can be assessed via a phone call by the Investigator or trained designee.

8.2.2. Ventilation Assistance-Free Survival (VAFS)

Ventilation Assistance-Free Survival is a composite endpoint of survival and severe and irreversible respiratory decline. The use of VAFS allows for the collection of survival data that is not impacted by survival prolongation from noninvasive or permanent ventilatory interventions

which can prolong life without impacting underlying disease progression. The composite endpoint of VAFS (Paganoni, 2014) that will be used as a secondary endpoint for this study will be defined as the first occurrence of:

- All-cause mortality
- First use of NIV for ≥ 22 hours per day for ≥ 10 consecutive days
- First use of PAV for ≥ 22 hours per day for ≥ 7 consecutive days

Information on the components of VAFS will be assessed at every dosing visit by the Investigator or designee (see Section 1.3) using the ventilator assistance utilization form. An attempt will be made to obtain information about survival at the Follow-up phone call.

8.2.3. Slow Vital Capacity (SVC)

Slow vital capacity is a spirometry technique that utilizes slow and gradual expulsion of air from the lungs. The full volume of expired air is measured as a proportion of the expected vital capacity of the patient based on biometric features such as age, height, and sex.

Slow vital capacity evaluation will be performed in the clinic by the Investigator, or any designee who has been properly trained for the evaluation, at screening and time points specified in the SoA (Section 1.3). When possible, it is highly recommended that all assessments be performed by the same assessor. In addition to SVC in the clinic, home SVC (where regionally available) should be performed using a provided spirometer and under the direction of study staff properly trained for the evaluation. In the event that an SVC measurement cannot be obtained in the clinic due to the COVID-19 pandemic, only home evaluation is required for that visit. Home SVC at screening should be performed after informed consent and after the patient has received training on the spirometer. For subsequent visits, including Day 1, home SVC should be performed within 3 days prior to the scheduled clinic visit.

8.2.4. Handheld Dynamometry (HHD)

Handheld dynamometry (HHD) (Shefner, 2016) is a procedure for quantitative strength testing. This testing will be conducted by the Investigator or any designee who has been properly trained for the quantitative muscle strength evaluation. When possible, it is highly recommended that all assessments be performed by the same assessor. Muscle strength testing will be performed on prespecified muscles in the upper and lower extremities bilaterally and the force measurements recorded. Handheld dynamometry will be assessed at the time points specified in the SoA (Section 1.3).

8.2.5. Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40)

The ALSAQ-40 is a validated ALS-specific instrument for measuring quality of life in patients with ALS. There are 40 items covering 5 discrete categories (physical mobility, activities of daily living and independence, eating and drinking, communication, and emotional reactions) (Section 10.7). Patients will be asked about the difficulties they have experienced in the past 2 weeks and the frequency of each event by selecting 1 of the 5 available options. The ALSAQ-40 will be self-assessed by patients.

8.2.6. EuroQoL 5 Dimensions (EQ-5D-5L)

The European Quality of Life (EQ-5D-5L) (Section 10.8) is a self-assessed, standardized instrument to measure health-related quality of life and has been used in a wide range of health conditions, including ALS (Schrag, 2000). The EQ-5D-5L consists of 2 pages: the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ VAS). At time points specified in the SoA (Section 1.3), or if a patient is not able to attend the scheduled onsite visit, EQ-5D-5L can be assessed via a phone call.

8.2.6.1. EQ-5D-5L Descriptive System

The descriptive system is a 5-component scale including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Section 10.8). Each level is rated on a scale that describes the degree of problems in that area.

8.2.6.2. EQ Visual Analogue Scale

The EQ-5D-5L VAS is an overall health state scale where the patient selects a number between 0 and 100 to describe the condition of their health, with 100 being 'The best health state you can imagine' and 0 being 'The worst health state you can imagine' (Section 10.8).

This information can be used as a quantitative measure of health outcome as judged by the individual respondents. Previously published studies by EuroQol Group members showed preliminary evidence of the instrument's feasibility, reliability, and validity.

8.2.7. Short Form Health Survey (SF-36)

The SF-36 (Section 10.8.2) is a 36-item self-report of health-related quality of life (Stewart, 1988; Ware, 1992). It contains 8 subscales measuring different domains of health-related quality of life: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. The SF-36 will be conducted at screening and at timepoints specified per SoA (Section 1.3) The 2 summary scores are the physical component summary and the mental component summary. There is no single overall score for the SF-36.

8.2.8. Treatment Satisfaction Questionnaire for Medication (TSQM)

The Treatment Satisfaction Questionnaire for Medication (TSQM-9) assesses 3 key dimensions of treatment satisfaction: Effectiveness (3 items); Convenience (3 items); and Global Satisfaction (3 items) (Bharmal, 2009). The instrument has been validated in chronic diseases including ALS (Meyer, 2019). The recall period for the TSQM is the previous 2 to 3 weeks or since last use. The TSQM-9 can be used to estimate total TSQM score, score for effectiveness, and score for convenience. The TSQM-9 will be administered at Day 1 and at timepoints specified in the SoA (Section 1.3).

8.3. Safety Assessments

The planned schedule for all safety assessments is provided in the SoA (Section 1.3).

8.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the following organs/body systems: skin, head, ears, eyes, nose, throat, neck, lymph nodes, chest, heart, abdomen, extremities, and musculoskeletal.
- An abbreviated physical examination will include, at a minimum, a body-system relevant examination based upon Investigator judgment and patient symptoms.
- Examiners should pay special attention to clinical signs related to previous serious illnesses.
- For consistency, all efforts should be made to have the physical examination performed by the same qualified study staff at each study visit.
- Additional physical examinations can be performed as medically indicated during the study at the Investigator's discretion.

8.3.2. Neurologic Examination

A general neurologic examination will be performed by the Investigator, Sub-Investigator, or designee at the scheduled visits (Section 1.3). The general neurologic examination includes assessments of the following systems: mental status, cranial nerves, deep tendon reflexes, power/strength, sensation, muscle fasciculations, and muscle atrophy.

8.3.3. Height and Weight

Body weight will be measured in pounds or kilograms. Height will be measured in inches or centimeters (Section 1.3).

8.3.4. Vital Signs

- Body temperature (°C or °F), pulse rate, respiratory rate, and systolic and diastolic blood pressure (mm Hg) will be assessed (Section 1.3).
- Blood pressure and pulse measurements will be assessed seated with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones). Ideally, the same arm for each patient should be used for measurements.

8.3.5. Electrocardiograms

- Single 12-lead electrocardiogram (ECG) will be performed at protocol specified visits in the SoA (Section 1.3) using an ECG machine to obtain heart rate and measures of PR, QRS, QT, and corrected QT intervals.
- Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. For patients who are unable to remain supine, the ECG procedure may occur in an inclined or seated position.

- The Investigator or Sub-Investigator will be responsible for reviewing the ECG to assess whether the ECG is within normal limits and determine the clinical significance of the results. These assessments will be recorded in the source documents and the eCRF.

8.3.6. Patient Safety Card

Before the first dose of study drug, a Patient Safety Card will be provided to patients to carry with them at all times. The card is provided to increase patient awareness of the risk of infections, especially meningococcal infection, and to promote quick recognition and disclosure of any potential signs or symptoms of infection experienced by patients during the course of the study and to inform patients on what actions must be taken if they are experiencing signs or symptoms of infection.

At each visit throughout the study, the study staff will ensure that the patient has the Patient Safety Card (Section 1.3).

8.3.7. Prior and Concomitant Medication Review

It is important for Investigators or a designee to review each medication the patient is taking before starting the study and at each visit (Section 1.3).

8.3.7.1. Prior Medications

Prior medications and/or vaccines (including vitamins, herbal preparations, and those discussed in the exclusion criteria [Section 5.2]) and procedures (any therapeutic drug, such as surgery/biopsy or physical therapy) that the patient takes or undergoes within 30 days before the start of screening or during the Screening Period before the first dose of study drug, as well as any meningococcal vaccine administered within the last 3 years, will be recorded in the patient's eCRF. Additionally, all medications or therapies ever used for treating ALS before the first dose of study drug must be collected.

8.3.7.2. Concomitant Medications

Concomitant medications (including any medication, vitamin, herbal preparation or supplement) and procedures (defined in Section 6.5) are those received on or after the first study treatment date (Day 1), including those started before Day 1 and continued after Day 1. At each study visit, patients should be questioned about any new medication or non-drug therapies or changes to concomitant medications and nondrug therapies since the last visit. Concomitant medications and non-drug therapies should be recorded in the source documents and the patient's eCRF. Concomitant medications must be recorded in the patient's source document/medical chart and eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Information regarding the use of ALS specific treatment including riluzole and edaravone must be collected. Meningococcal vaccination and antibiotics administered for prophylaxis of meningococcal infection (if applicable) will also be recorded.

Any concomitant medication deemed necessary for the patient's care during the study, or for the treatment of any AE, along with any other medications, other than those listed as disallowed medications in Section 6.5.1.3, may be given at the discretion of the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding all medications are recorded in full in the patient's source document/medical chart and eCRF.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

8.3.8. Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3 for the timing and frequency).
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 8 weeks after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and Alexion notified.
  - All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the Laboratory Manual and the SoA.
  - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the Investigator (eg, serious adverse event (SAE) or AE or dose modification), then the results must be recorded in the CRF.

8.3.9. Suicidal Ideation and Behavior Risk Evaluation

Patients being treated with a study drug for a neurologic indication should be evaluated prospectively for suicidal ideation or behavior during the study.

In this study, the Columbia-suicide severity rating scale (C-SSRS) will be used to monitor suicidal ideation and behavior. The Baseline/Screening version (Section 10.11) will assess lifetime risk as well as risk in the past 12 months. Intervention-emergent suicidal ideation and behavior will be monitored using the C-SSRS-Since Last Visit version (Section 10.12).

The C-SSRS will be performed by the Investigator or an appropriately trained designee at visits specified in the SoA (Section 1.3) to ensure that patients who are experiencing suicidal thoughts or behavior are properly recognized and adequately managed or referred for further evaluation. Additional C-SSRS assessments are permitted as needed.

8.3.10. Pregnancy

Pregnancy testing must be performed on all WOCBP at protocol-specified time points in the SoA (Section 1.3). Pregnancy tests (local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC) may also be performed at any time during the study at the Investigator's discretion.

WOCBP must have a negative pregnancy test (serum if required per country regulations) before study drug administration.

- Details of all pregnancies in female patients and, if indicated, female partners of male patients will be collected after the start of study drug and until the termination of the pregnancy.
- If a pregnancy is reported, the Investigator should inform Alexion within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs. Pregnancy alone is not considered an AE.
- If a patient becomes pregnant, the study drug must be immediately discontinued, and Alexion must be notified as per Section 10.4. Each pregnancy will be followed to term and Alexion notified regarding the outcome (Section 10.4.3).

8.4. Adverse Events and Serious Adverse Events

The definitions of AEs and serious SAEs are specified in Section 10.3.

Adverse events will be reported to the Investigator by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study drug or study procedures, or that caused the patient to discontinue the study drug (Section 7).

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the last visit specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to Alexion or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 1.3. The Investigator will submit any updated SAE data to Alexion within 24 hours of awareness.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify Alexion.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs and AEs of special interest (AESI; as defined in Section 8.4.5) will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Every effort will be made to undertake protocol-specified safety follow-up procedures. Further information on follow-up procedures is provided in Section 10.3.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to Alexion of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study drug under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- Suspected unexpected serious adverse reactions must be reported according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from Alexion will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5. Adverse Events of Special Interest

Meningococcal infections will be collected as AESIs.

8.5. Treatment of Overdose

For this study, any dose of study drug greater than that specified in the protocol will be considered an overdose. If dose cannot be established during the Randomized Controlled Period due to blinding, suspected overdose should be defined by volume administered.

Accidental overdose or suspected overdose without any association with laboratory abnormalities or clinical symptoms should not be considered as an AE. Overdose must be reported by the Investigator within 24 hours to Alexion regardless of whether an AE occurred.

The Sponsor does not recommend specific treatment for an overdose or suspected overdose.

In the event of an overdose or suspected overdose, the Investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the patient for any AE/SAE
- Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
- For unblinded patients, document the quantity of the excess dose as well as the timing of the overdose in the CRF.

Decisions regarding dose interruptions will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the patient.

8.6. Pharmacokinetics and Pharmacodynamics

- Blood samples for determination of serum drug concentrations and PD assessments will be collected before and after administration of study drug at the time points specified in the SoA (Section 1.3).
- Cerebrospinal fluid (CSF) samples for PK and PD assessments are optional at protocol-specified time points (Section 1.3). Samples will only be obtained from patients who consent to CSF collection (CSF Cohort). Collection should be performed at the screening visit after all other assessments are complete and eligibility has been confirmed.
  - Lumbar punctures will be performed to collect CSF samples and may only be performed on patients who have consented to CSF sample collection. Patients who are on therapeutic doses of anticoagulants will be deemed ineligible for the optional lumbar puncture procedures in this study. In addition, patients may be deemed ineligible to undergo lumbar puncture at the discretion of the Investigator after consideration of medical history, physical examination findings, laboratory assessments required as part of the SoA or other factors.
- Instructions for the collection and handling of biological samples will be provided by Alexion. The actual date and time (24-hour clock time) of each sample will be recorded on the eCRF and the central laboratory requisition form.
- Additional information on sample collection, including blood volume requirements, is provided in the Laboratory Manual.

- Baseline and trough PK and PD blood samples will be collected at predose, within 90 minutes before administering study drug at visits specified in the SoA (Section 1.3). The predose blood sample may be drawn through the venous access created for the dose infusion, prior to administration of the dose.
- Postdose PK and PD blood samples will be collected postdose, within 60 minutes after completing study drug infusion. The postdose blood samples will be drawn from the patient's opposite, noninfused arm.
- Blood samples at a nondosing visit can be collected at any time.
- In the event of an unscheduled visit, PK and PD blood sample will be collected as soon as possible.

8.7. Genetics

There are no prespecified genetic analyses in this study.

8.8. Biomarkers

8.8.1. Biomarker Research

Blood and urine samples for biomarker research will be collected from all patients, as described in Section 8.6, at the time points specified in the SoA (Section 1.3). Blood samples for biomarkers will be collected before administration of study drug, and biomarker urine samples may be collected at any time during the scheduled visit.

CSF samples are optional samples for biomarker research and should only be collected from patients who have consented to CSF sample collection. For biomarker CSF sample collection, refer to Section 8.6 and follow the same instructions on lumbar punctures for PK/PD assessments.

Biomarkers will be measured and include, but are not limited to, assessments of the following:

- Markers of neurodegeneration, such as neurofilament light chain (NfL)
- Complement proteins
- Markers of neuroinflammation, such as levels of proinflammatory cytokines and inflammatory cells

8.8.2. Future Biomarker Research

Blood samples for DNA and RNA isolation will be collected from patients who have consented to participate in the future genetic analysis component of the study. Future DNA and RNA testing on these samples includes, but is not limited to, specific candidate genes/genome-wide analysis.

Remaining samples from PK, PD, immunogenicity, and biomarker testing will be stored for future biomarker research. Analyses may be performed on biomarker variants thought to play a role in ALS activity/progression or treatment response to ravulizumab. These samples may also be used to develop methods, assays, prognostics and/or companion diagnostics related to the

study drug target, disease process, pathways associated with disease state, other complement-related diseases, and/or mechanism of action of the study drug.

Samples may be stored for a maximum duration according to local regulations following the last patient's last visit for the study at a facility selected by Alexion to enable further analyses.

8.9. Immunogenicity Assessments

Antidrug antibodies (ADAs) to study drug will be evaluated in serum samples collected predose (within 5 to 90 minutes prior to the start of infusion of study drug) from all patients according to the SoA (Section 1.3).

Additionally, serum samples should also be collected at the final visit from patients who discontinued study drug or were withdrawn from the study.

Serum samples will be screened for antibodies binding to ravulizumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to ravulizumab and/or further characterize the immunogenicity of ravulizumab.

The detection and characterization of antibodies to ravulizumab will be performed using a validated assay method by or under the supervision of Alexion. Samples may be further characterized to determine the titer and the presence of neutralizing antibodies if deemed necessary. Samples may be stored for a maximum duration according to local regulations following the last patient's last visit for the study at a facility selected by Alexion to enable further analysis of immune responses to ravulizumab.

8.10. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data associated with medical encounters will be collected in study eCRFs by the Investigator and study-site personnel for all patients throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected, which may be used to conduct exploratory economic analyses, include the following:

- Number of surgeries, and other selected procedures (inpatient and outpatient)
- Number and duration of hospitalizations
- Use of ventilator use and duration of use
- Use of wheelchair
- Use of feeding tube

9. STATISTICAL CONSIDERATIONS

Statistical methods described in this section will be further detailed in a separate Statistical Analysis Plan (SAP). The SAP will be developed and finalized prior to the database lock for the Randomized Controlled period. Statistical analyses will include tabulations of summary data, inferential analyses, by-patient listings and figures. Inference from efficacy analyses will be based on a 2-sided Type I error (α) = 5% unless stated otherwise. The summary statistics for continuous variables will include but not be limited to the number of patients, mean, standard deviation, minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented. The baseline value for analysis and reporting will be based on the last nonmissing measurement on or prior to the first dose of study drug unless stated otherwise. The treatment groups for analysis and reporting will be based on the conventions outlined in Table 8. A 'Total' treatment group will be formed to report demographics, baseline characteristics, and other prestudy information including, medical and ALS history, and prior medications and SAEs captured between screening and first infusion. Details for imputation of efficacy data will be described in the SAP. Missing safety data will not be imputed.

Analyses will be performed using the SAS® software Version 9.4 or higher.

9.1. Statistical Hypotheses

9.1.1. Primary Hypothesis

The primary null hypothesis is that the effect of ravulizumab is no different than placebo in functional decline measured by the change from baseline in ALSFRS-R total score at Week 50. The alternative hypothesis is that ravulizumab will slow the disease progression by reducing the decline from baseline in ALSFRS-R total score at Week 50 compared to placebo.

9.1.2. Secondary Hypotheses

The null hypotheses associated with the secondary objectives are that ravulizumab is no different than placebo for the respective endpoints; the alternative hypotheses are described below:

1. **Time to VAFS**: The alternative hypothesis is that treatment with ravulizumab will prolong the time to VAFS compared to placebo.
2. **Change in SVC**: The alternative hypothesis is that treatment with ravulizumab will slow the decline from baseline in SVC at Week 50 compared to placebo.
3. **Change in muscle strength (HHD)**: The alternative hypothesis is that treatment with ravulizumab will slow the decline from baseline in muscle strength at Week 50 compared to placebo.
4. **Neurofilament light chain (NfL) concentration:** The alternative hypothesis is that treatment with ravulizumab will lower the NfL concentration at Week 50 compared to placebo.

9.2. Sample Size Determination

The sample size calculations were based on information extracted from the PRO-ACT (Pooled Resource Open-Access ALS Clinical Trials, https://nctu.partners.org/ProACT) database

consisting of data pooled from 23 Phase 2/3 ALS clinical studies. Approximately 354 patients will be randomized to ravulizumab or placebo in a 2:1 ratio.

The mean change in ALSFRS-R total score in the placebo arm at Week 50 is estimated as -14.3 (assuming a monthly linear slope of decline of 1.19 calculated based on the proposed study inclusion criteria). Assuming a 30% relative reduction in monthly slope in the ravulizumab group, which is considered a clinically meaningful treatment effect (Castrillo-Viguera, 2010; Writing Group for Edaravone ALS Study, 2017), the mean change in ALSFRS-R total score at Week 50 is estimated as -10. A common standard deviation of 10.3 was estimated for the change from baseline in ALSFRS-R total score. A total of 282 patients will be required to ensure at least 90% nominal power based on a 2-sided t-test (Type I error = 0.05) for detecting a non-zero treatment effect for ALSFRS-R (defined as the difference between ravulizumab and placebo in the mean change from baseline in ALSFRS-R total score at Week 50). The total sample size is estimated as 354 after adjusting for a 20% dropout (Cudkowicz, 2013). Furthermore, assuming approximately 82% 1-year survival rate for placebo group and 50% relative reduction in hazard ratio for mortality due to treatment with ravulizumab, this sample size will provide at least 90% nominal power based on the primary analysis (CAFS).

9.2.1. Stratification

Amyotrophic lateral sclerosis is a heterogeneous disease the progression of which is impacted by intrinsic disease factors and concomitant ALS medication use. Patients with bulbar onset ALS are well described to have a poorer prognosis than other ALS patients (Swinnen, 2014). To control this heterogeneity the study will be stratified based on known prognostic factors and concomitant ALS medication use.

The site of muscle weakness onset (bulbar vs other) and riluzole use at study entry will be used as stratification factors (Cudkowicz, 2013). In addition, patients on stable edaravone will also be employed in the stratification scheme. It is anticipated that a relatively low percentage of patients will be on edaravone without concomitant riluzole use; the stratification scheme based on this assumption is provided in Table 7.

Table 7: Stratification Scheme

Stratum	Bulbar Onset	Riluzole Use at Screening	Edaravone Use at Screening
1	No	No	Yes, No
2	No	Yes	Yes
3	No	Yes	No
4	Yes	No	Yes, No
5	Yes	Yes	Yes
6	Yes	Yes	No

9.3. Populations for Analyses

Analysis sets are defined in Table 8.

Table 8: Analysis Sets

Population	Description
Randomized Set	All randomized patients grouped by randomized treatment group (for reporting disposition, demographics, and baseline characteristics)
Full Analysis Set (FAS)	All randomized patients who receive at least 1 dose of study drug grouped by randomized treatment group (for reporting efficacy data)
Per Protocol Set	All randomized patients who receive at least 1 dose of study drug and without any major protocol deviations.
Safety Set (SS)	All patients who receive at least 1 dose of study drug grouped by treatment actually received (for reporting exposure and safety data). For a patient to be analyzed according to the treatment they actually received and not according to the randomization schedule, they would have to receive that treatment for the entire duration of Randomized Controlled Period.
Pharmacokinetic Analysis Set (PKAS)	All patients who receive at least 1 dose of study drug and have at least 1 postdose pharmacokinetic sample
Open-label Extension Set	All patients who receive at least 1 dose of ravulizumab starting from Week 50 onward (for reporting all data from the Open-Label Extension Period)

9.4. Statistical Analyses

9.4.1. Enrollment and Disposition

The number of patients screened, screen failures, and randomized patients will be presented. Enrollment information will be presented by stratification factor and treatment group. Number of patients discontinued and reasons for discontinuation from the Randomized Controlled Period, Open-Label Extension Period, and the overall study will be summarized.

9.4.2. Demographics, Baseline Characteristics, Inclusion and Exclusion Criteria, and Protocol Deviations

All demographic information and baseline characteristics will be reported by treatment group and overall. No statistical test will be performed for homogeneity among treatment groups. The number and percentage of patients not meeting specific inclusion or exclusion criterion will be summarized. Similar summary will be provided for major protocol deviations based on prespecified categories.

9.4.3. Medical/Surgical History, Physical Examination, and Amyotrophic Lateral Sclerosis History

The medical and surgical history will be summarized by System Organ Class (SOC) and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 or higher. Amyotrophic lateral sclerosis history and abnormal physical examination will also be summarized.

9.4.4. Prior and Concomitant Medications

For analysis and reporting purpose, any medication started prior to first dose of study drug will be considered as prior medication and any medication taken by a patient that overlaps with the intake of study drug will be considered as concomitant medication. All prior and concomitant medications including ALS-specific medications during the study, if any, will be summarized.

9.4.5. Efficacy Analyses

9.4.5.1. Analyses of Primary Efficacy Endpoint

9.4.5.1.1. Primary Analysis

The analysis of the primary endpoint will be conducted based on the Full Analysis Set. For patients who do not survive until Week 50, ALSFRS-R total scores will be missing which, if not adequately accounted for, may bias the evaluation of clinical benefit. A joint rank analysis (CAFS) recommended in the Food and Drug Administration guidance document on ALS (Sep 2019) that combines deaths and ALSFRS-R will be performed as the primary analysis. The CAFS is an analysis that evaluates function while accounting for missing data due to deaths in ALS where CAFS ranks patients' clinical outcomes based on survival time and change in the ALSFRS-R total score (Berry, 2013). Each patient will be ranked either based on their last available change from baseline in ALSFRS-R total score within Week 50 or the time to death.

The analysis of CAFS ranks will be based on an analysis of covariance model. The model will include the CAFS ranks as the dependent variable and following list of independent variables: treatment indicator (0 = placebo, 1 = ravulizumab), age, sex, baseline ALSFRS-R total score, baseline SVC, time from muscle weakness onset, and the stratification factors. A p-value less than the Type I error = 0.05 associated with the higher mean rank in ravulizumab group compared to placebo will indicate a statistically significant treatment benefit.

9.4.5.1.1.1. Alternate Primary Analysis

Per Committee for Medicinal Products for Human Use recommendation, an MMRM (mixed-effects model repeated measures) based analysis of the primary endpoint will be conducted for EMA submission. For this analysis, the missing ALSFRS-R scores due to deaths will be imputed as zero (worst score imputation) and other missing data will be imputed according to placebo-based mean trajectories. The model will include the change from baseline in ALSFRS-R total score at each nominal visit as the dependent variable and the following list of independent variables as fixed effects: actual time on study (months), the interaction between time and treatment (0 = placebo, 1 = ravulizumab), age, sex, baseline ALSFRS-R total score, baseline SVC, time from muscle weakness onset, and the stratification factors. In addition, the patient-specific random slope will be added to the model with an unstructured variance-covariance matrix to model the correlations among repeated measurements within each patient. Other covariance structures will be implemented if a convergence issue occurs (details to be provided in SAP). The Kenward-Rogers method will be used to estimate the denominator degrees of freedom. A p-value less than the Type I error = 0.05 associated with the higher mean change in ALSFRS-R total score in the ravulizumab group compared to placebo will indicate a statistically significant treatment benefit.

9.4.5.1.2. Sensitivity Analyses

To establish the robustness of the primary analysis and to quantify the treatment effect magnitude, the following sensitivity analyses will be conducted.

9.4.5.1.2.1. Mixed-Effect Model for Repeated Measures (MMRM) Sensitivity Analysis

The mixed-effect model for repeated measures (MMRM) analysis will be conducted using all available longitudinal data (either complete or partial). The model will include the change from baseline in ALSFRS-R total score at each nominal visit as the dependent variable and the following list of independent variables as fixed effects: actual time on study (months), the interaction between time and treatment (0 = placebo, 1 = ravulizumab), age, sex, baseline ALSFRS-R total score, baseline SVC, time from muscle weakness onset, and the stratification factors. In addition, the patient-specific random slope will be added to the model with an unstructured variance-covariance matrix to model the correlations among repeated measurements within each patient. Other covariance structures will be implemented if a convergence issue occurs (details to be provided in SAP). The Kenward-Rogers method will be used to estimate the denominator degrees of freedom.

No imputation for the missing data will be performed after discontinuation from the study assuming the data are missing at random (MAR). The treatment effect will be evaluated via the estimated treatment-by-visit interaction term at Week 50.

9.4.5.1.2.2. MMRM Sensitivity Analysis With Placebo-based Imputation

To examine the deviation from MAR assumption, another MMRM analysis will be considered based on the Missing Not At Random mechanism for the missing data. The missing ALSFRS-R total scores after discontinuation of ravulizumab during the Randomized Controlled Period will be imputed based on the assumption that those patients will follow the trajectory of outcomes similar to the placebo arm. Patients who prematurely discontinue from the placebo arm will be assumed to have unobserved outcomes similar to that of placebo patients who remain on their randomized treatment. Missing data due to deaths will not be imputed (see Section 9.4.5.1.1.1 for the analysis related to the worst score imputation due to deaths).

9.4.5.1.2.3. Vonesh Shared Parameter Model

In addition, parametric modeling (Vonesh shared parameter model) may also be performed (Vonesh, 2006). In this model, both the longitudinal changes in the ALSFRS-R total score and the time to death are modeled together assuming a patient-specific random slope for ALSFRS-R trajectory. The model also assumes that a patient's survival time has a Weibull distribution with a hazard that is a function of the patient's ALSFRS-R trajectory; the treatment effect of ravulizumab on ALSFRS-R and mortality will be estimated separately from this joint model.

9.4.5.1.2.4. Sensitivity Analysis by Only Including the Stratification Factors

An analysis similar to the primary analysis for EMA submission (Section 9.4.5.1.1.1) will be conducted by incorporating the treatment and the stratification factors only and excluding all other covariates.

9.4.5.2. Analyses of Secondary Efficacy Endpoint(s)

Analysis of the secondary endpoints will be performed as follows:

- **Time to VAFS**: The treatment effect on the time to VAFS will be analyzed based on a Cox's regression model treatment as a fixed effect adjusting for age, sex, baseline ALSFRS-R total score, baseline SVC, disease duration, and the stratification factor.

  The components of VAFS will be analyzed separately using similar models.

- **Change in SVC**: The treatment effect on SVC will be evaluated based on a MMRM with the change from baseline in SVC percent predicted as the dependent variable and following list of independent variables as fixed effects: actual time on study (months), time and treatment interaction, age, sex, baseline ALSFRS-R total score, baseline SVC, disease duration, and the stratification factor. In addition, the patient-specific random slope will be added to the model with an unstructured variance-covariance matrix. The Kenward-Rogers method will be used to estimate the denominator degrees of freedom. No imputation for the missing data will be performed after discontinuation assuming the data are MAR. This analysis will be based on the endpoint defined as the change from baseline in SVC based on the in-clinic assessment or the at-home assessment when in-clinic assessment is not available.

- **Change in muscle strength (HHD)**: For each patient, a megascore will be calculated at each visit by summing scores from all muscles. The scores will be normalized by the baseline megascore multiplied by 100 (hence the baseline score is always 100%). The change from the baseline score of 100% will be used for analysis. The treatment effect on HHD will be evaluated based on a MMRM with the change from baseline in HHD as the dependent variable and following list of independent variables as fixed effects: actual time on study (months), time and treatment interaction, age, sex, baseline HHD megascore, baseline ALSFRS-R total score, baseline SVC, disease duration, and the stratification factor. In addition, the patient-specific random slope will be added to the model with an unstructured variance-covariance matrix. The Kenward-Rogers method will be used to estimate the denominator degrees of freedom. No imputation for the missing data will be performed after discontinuation assuming the data are MAR.

- **Neurofilament light chain (NfL) concentration**: The treatment effect of ravulizumab on NfL vs placebo will be evaluated based on a MMRM with log(NfL) as the response variable and with adjustments for treatment, age, and log(baseline NfL). The model will further include a visit-by-treatment interaction. An unstructured covariance matrix will be used.

9.4.5.3. Analyses of Exploratory Endpoint(s)

- **Time to first instance of SVC < 50% predicted:** The treatment effect on the time to first instance of SVC < 50% will be evaluated based on a Cox's regression model with treatment as a fixed effect adjusting for age, sex, baseline ALSFRS-R total score, baseline SVC, disease duration, and the stratification factor.

- **Change in SF-36:** The treatment effect on SF-36 physical component score (PCS) will be evaluated based on a MMRM with the change from baseline in SF-36 PCS as the dependent variable and following list of independent variables as fixed effects:

categorical visits, treatment and visit interaction, age, sex, baseline SF-36 PCS, baseline ALSFRS-R total score, baseline SVC, disease duration, and the stratification factor. The Kenward-Rogers method will be used to estimate the denominator degrees of freedom. An unstructured within subject variance-covariance matrix will be used. No imputation for the missing data will be performed after discontinuation assuming the data are MAR.

Similar analysis will be based on SF-36 mental component score (MCS).

- **Change in EQ-5D-5L index score:** The treatment effect on EQ-5D-5L index score will be evaluated based on a MMRM with the change from baseline in the index score as the dependent variable and following list of independent variables as fixed effects: categorical visits, treatment and treatment and visit interaction, age, sex, baseline EQ-5D-5L index score, baseline ALSFRS-R total score, baseline SVC, disease duration, and the stratification factor. The Kenward-Rogers method will be used to estimate the denominator degrees of freedom. An unstructured within subject variance-covariance matrix will be used. No imputation for the missing data will be performed after discontinuation assuming the data are MAR.
- **Change in EQ-5D-5L VAS score:** The treatment effect on EQ-5D-5L VAS score will be evaluated based on a MMRM with the change from baseline in the index score as the dependent variable and following list of independent variables as fixed effects: categorical visits, treatment and treatment and visit interaction, age, sex, baseline EQ-5D-5L VAS score, baseline ALSFRS-R total score, baseline SVC, disease duration, and the stratification factor. The Kenward-Rogers method will be used to estimate the denominator degrees of freedom. An unstructured within subject variance-covariance matrix will be used. No imputation for the missing data will be performed after discontinuation assuming the data are MAR.
- **Change in ALSAQ-40 score:** A single index score is created by adding all of the responses (0, 1, 2, 3, or 4) of 40 items of ALSAQ-40, dividing this total score by the maximal score of 160 and finally multiplying by 100. An index score of 0 indicates perfect health and 100 indicates worst possible health status. The treatment effect on ALSAQ-40 index score will be evaluated based on a MMRM with the change from baseline in the index score as the dependent variable and following list of independent variables as fixed effects: categorical visits, treatment and treatment and visit interaction, age, sex, baseline ALSAQ-40 index score, baseline ALSFRS-R total score, baseline SVC, disease duration, and the stratification factor. The Kenward-Rogers method will be used to estimate the denominator degrees of freedom. An unstructured within subject variance-covariance matrix will be used. No imputation for the missing data will be performed after discontinuation assuming the data are MAR.
- **Increase in KSS:** The proportion of patients with any increase from the baseline KSS at Week 50 will be compared between ravulizumab and placebo. A logistic regression analysis will be conducted with treatment indicator as the fixed effect adjusting for the baseline KSS. An estimate of the odds ratio and 95% confidence interval will be generated.

9.4.5.4. Multiplicity Adjustment

If the primary analysis is statistically significant, the study wise Type I error will be controlled using Hochberg method for multiplicity adjustment of the p-values corresponding to the two secondary endpoints (VAFS and change in SVC).

9.4.6. Safety Analyses

The safety and tolerability of ravulizumab will be assessed based on AEs, clinical laboratory findings, vital sign findings, and ECG abnormalities. Safety analyses will be performed on the Safety Set and Open-label extension Set based on the study period under consideration.

9.4.6.1. Analysis of Adverse Events

Analysis and reporting for AEs will be based on treatment-emergent AEs, including treatment-emergent SAEs (TESAEs) defined as an AE with onset on or after first dose of study drug administration in the Randomized Controlled Period. Treatment-emergent AEs and TESAEs will be summarized by MedDRA SOC and Preferred Term and by relationship to the study drug; TEAEs will also be summarized by severity. Patient-years adjusted event rates will be generated to characterize long-term safety profile.

9.4.6.2. Analysis of Clinical Laboratory Parameters, Vital Sign Measurements, Weight, and Electrocardiogram Parameters

Laboratory measurements as well as their changes from baseline at each visit and shift from baseline, if applicable, will be summarized descriptively. Weight, ECG, and vital signs will also be summarized using descriptive analyses.

9.4.6.3. Other Safety Analyses

The number and percentage of patients in each of the C-SSRS categories and shift analyses will be presented. Results from pregnancy tests will be summarized. Number and percentage of patients in each category of the neurologic assessments will be summarized.

9.4.7. Analysis of Pharmacokinetics and Pharmacodynamics, and Antidrug Antibody Analyses

Individual serum concentration data for all patients who receive at least 1 dose of the study drug and have at least 1 post-dose PK sample will be used to derive PK parameters for ravulizumab.

Graphs of mean serum concentration-time profiles will be constructed. Graphs of serum concentration-time profiles for individual patients may also be provided. Actual dose administration and sampling times will be used for all calculations. Descriptive statistics will be calculated for serum concentration data at each sampling time, as appropriate. Assessment of population-PK may be considered using data from this study or in combination with data from other studies.

Pharmacodynamic analyses will be performed for all patients who receive at least 1 dose of ravulizumab and who have evaluable PD data.

Descriptive statistics will be presented for all ravulizumab PD endpoints at each sampling time. The PD effects of ravulizumab will be evaluated by assessing the absolute values and changes

and percentage changes from baseline in free C5 serum concentrations over time, as appropriate. Assessments of ravulizumab PK/PD relationships may be explored using data from this study or in combination with data from other studies.

For assessment of immunogenicity, the presence of confirmed positive ADAs will be summarized. Additionally, following confirmation of positive ADAs, samples will be assessed for ADA titer and presence of neutralizing antibodies.

9.4.8. Analysis of Exploratory Biomarkers

For exploratory biomarker analyses, summary statistics will be presented for observed values, change and percentage change from baseline. Additional details will be provided in the SAP.

9.5. Interim Analysis

One interim analysis for futility will be conducted by an IDMC to determine if the study is unlikely to meet its objective. If futility criteria are met, the study (both the Randomized Controlled Period and Open-Label Extension Period) may be terminated early, thereby limiting patient exposure to an ineffective drug.

This interim analysis will be conducted when approximately 33% of patients complete the Week 26 visit. The futility assessment will be performed using all available ALSFRS-R data.

The criteria for futility will be prespecified in the IDMC charter or the interim analysis plan.

9.6. Delayed-Start Analysis of Long-term ALSFRS-R

To provide additional evidence of a disease modifying effect of treatment with ravulizumab on disease progression, a delayed start analysis will be conducted based on an MMRM approach and by incorporating all data from the Randomized Controlled Period (referred to as early start) and the first 50 weeks of the Open-Label Extension Period (referred to as delayed start). In this model, the patients initially randomized to placebo will be assumed to have different ALSFRS-R slopes for the Randomized Controlled Period and the Open-Label Extension Period whereas for the patients randomized to ravulizumab, a slope common to both periods will be assumed. The treatment effects will be quantified by the estimated differences between the groups based on their original treatment arms (ravulizumab vs placebo) for both early and delayed start periods; the estimated difference at the end of the delayed start period will be assessed for noninferiority compared to the estimated difference at the end of the early start period (Liu-Seifert, 2015). Further details will be provided in the SAP.

9.7. Data Monitoring Committee

The safety and efficacy data of this study will be monitored by an IDMC appointed by Alexion. Minimally, the IDMC members will include external physicians and a statistician who have expertise in both the field of ALS and clinical study conduct and with no direct relationship to the study. Each member of the IDMC will be required to sign an agreement, including confidentiality and financial disclosure statements, assuring no conflicts of interest as a condition for membership on the committee.

All statistical analyses presented to the IDMC will be performed by an independent statistical center. The IDMC will independently evaluate safety and efficacy data from the study periodically and at prespecified enrollment-dependent time points. The IDMC will make recommendations regarding study modification or continuation based on their review and in accordance with the agreed upon IDMC charter. Recommendations from the IDMC will be relayed to an Alexion Executive Representative who will make a determination about implementing recommendations to modify or discontinue the study. All appropriate regulatory authorities and ethics committees will be notified of significant actions taken as a result of IDMC recommendations. To maintain study integrity and to prevent the potential introduction of bias, all study team members will remain blinded until the final analysis of the Randomized Controlled Period is conducted. Details of this process will be documented in the IDMC charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will notify the IRB/IEC of deviations from the study protocol or GCP as defined by UK legislation as a serious breach or as required by IRB/IEC procedures.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and Sub-Investigators will provide Alexion with sufficient, accurate financial information as requested to allow Alexion to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- It is the responsibility of the investigator to obtain signed informed consent from all study participants prior to any study-related procedures including screening assessments. If a patient is not able to sign and date the ICF due to physical constraint, verbal consent given by the patient and witnessed by a third party or legally authorized representative is allowed to complete the ICF for the patient.
- The Investigator or his/her representative will explain the nature of the study (including but not limited to the objectives, potential benefits and risk, inconveniences, and the participant's rights and responsibilities) to the participant or his/her legally authorized representative, defined according to local and country regulations where the study is taking place, and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative, will be required to sign a statement of informed consent, or a certified translation if applicable, that meets the requirements of 21 CFR 50, local regulations, EU General Data Protection Regulation (GDPR), ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that informed consent was obtained before the participant was screened in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF(s).
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the signed informed consent documentation (ie, a complete set of participant information sheets and fully executed signature pages) must be provided to the participant or the participant's legally authorized representative. This document may require translation into the local language. Signed consent forms must remain in each participant's study file and must be available for verification at any time.

Participants who are rescreened (Section 5.4) are not required to sign a new ICF unless the prior ICF is dated outside of the current screening window.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The participant will be required to document agreement to allow any remaining specimens to be used for this purpose. Participants who decline to participate in this optional research will document that they do not agree in this section.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by Alexion. Any participant records or datasets that are transferred to Alexion will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

- The participant must be informed that his/her personal study-related data will be used by Alexion in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Alexion, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

Study-related information and study results may be posted on publicly accessible clinical study databases (eg, the US website www.clinicaltrials.gov or the EU website www.clinicaltrialsregister.eu), as appropriate, and in accordance with national, regional, and local regulations.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRF unless transmitted to Alexion or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after the last marketing application approval, or if not approved, 2 years following the discontinuance of the study drug, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Alexion. No records may be transferred to another location or party without written notification to Alexion.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The Investigator or designee will prepare and maintain adequate and accurate source documents (eg, medical records, ECGs, AE and concomitant medication reporting, raw data collection forms) designed to record all observations and other pertinent data for each patient.
- Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available. Source documents are filed at the Investigator's site.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the first participant is consented.

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of Alexion. Study sites will be closed after the study is completed or following the decision to close or terminate the study. A study site is considered closed when all patients have completed the end of study or ED visit, all data have been collected and entered into electronic data capture (EDC), all required documents and study supplies have been collected, and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by Alexion or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Alexion's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study drug development

If the study is prematurely terminated or suspended, Alexion shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

10.1.9. Publication Policy

The full terms regarding publication of the results of this study are outlined in the applicable Clinical Study Agreement.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 9 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study drug administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study drug decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Women of childbearing potential should only be enrolled after a negative serum or urine pregnancy test. Urine pregnancy testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC and should be performed per the time points specified in the SoA (Section 1.3).
- Investigators must document their review of each laboratory safety report.

Table 9: Protocol-Required Laboratory Assessments

Chemistry Panel	**Others**
Sodium Potassium Chloride Bicarbonate Blood urea nitrogen Creatinine Glucose Alkaline phosphatase Alanine amino transferase (ALT) Aspartate amino transferase (AST) Total and direct bilirubin Albumin Total protein Uric acid Calcium Magnesium	HIV (1 and 2) testing Human chorionic gonadotropin (β-HCG) pregnancy test (as needed for women of childbearing potential)[a] Follicle-stimulating hormone (FSH)[b] Coagulation profile (including international normalized ratio [INR], activated partial thromboplastin time [APTT])[c]
Complete Blood Count (CBC) & Differential	
White blood cell count (WBC) WBC differential Red blood cell count (RBC) RBC mean corpuscular volume (MCV) RBC distribution width Hemoglobin Hematocrit Platelet count	
Urinalysis	
Appearance Specific gravity pH Protein Blood Glucose Ketone Bilirubin Urobilinogen Nitrite	

[a] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committees.
[b] FSH to be performed at Screening in selected female patients to confirm postmenopausal status.
[c] Coagulation to be performed at Screening for all patients and at Week 18 and Week 42 for patients in CSF cohort.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Adverse Event Definition

Adverse Event Definition
• An AE is any untoward medical occurrence in a patient, temporally associated with the use of study drug, whether or not considered related to the study drug. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.
Events <u>NOT</u> Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (eg, hospitalization for elective surgery if planned before the signing the ICF, admissions for social reasons or for convenience). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • A medication error (including intentional misuse, abuse, and overdose of the product) or use other than what is defined in the protocol is not considered an AE unless there is an untoward medical occurrence as a result of a medication error. • Cases of pregnancy that occur during maternal or paternal exposure to study intervention are to be reported within 24 hours of Investigator/site awareness. Data on fetal outcome and breastfeeding will be collected for regulatory reporting and safety evaluation. • Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

10.3.2. Serious Adverse Event Definition

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as an AE that, at any dose:
1. Results in death
2. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
4. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
5. Is a congenital anomaly/birth defect
6. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of Adverse Event and/or Serious Adverse Event

Adverse Event and Serious Adverse Event Recording
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE or SAE information in the CRF. • It is not acceptable for the Investigator to send photocopies of the patient's medical records to Alexion in lieu of completion of the AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by Alexion. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to Alexion. • The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories from National Cancer Institute CTCAE v5.0, published 27 Nov 2017:

- Grade 1: Mild (awareness of sign or symptom, but easily tolerated)
- Grade 2: Moderate (discomfort sufficient to cause interference with normal activities)
- Grade 3: Severe (incapacitating, with inability to perform normal activities)
- Grade 4: Life-threatening
- Grade 5: Fatal

Changes in the severity of an AE should be documented to allow an assessment of the AE duration at each level of intensity to be evaluated. Adverse events characterized as intermittent require documentation of onset and duration of each episode, if the severity of the intermittent event changes.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between the study drug and each occurrence of each AE or SAE. An Investigator causality assessment must be provided for all AEs (both nonserious and serious). This assessment must be recorded in the eCRF and on any additional forms, as appropriate. The definitions for the causality assessments are as follows:
  - **Not related: There is no reasonable possibility the study intervention caused the adverse event.**
    - **The adverse event has a more likely alternative etiology; it may be due to underlying or concurrent illness, complications, concurrent treatments, or effects of another concurrent drug.**
    - **The event does not follow a reasonable temporal relationship to administration of the study intervention.**
  - **Related: There is a reasonable possibility the study intervention caused the adverse event.**
    - **The adverse event has a temporal relationship to the administration of the study intervention.**
    - **The event does not have a likely alternative etiology.**
    - **The event corresponds with the known pharmaceutical profile of the study intervention.**
  - **There is improvement on discontinuation and/or reappearance on rechallenge.**
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated.
- This protocol will use the current Investigator's Brochure as the Reference Safety Document. The expectedness and reporting criteria of an SAE will be determined by Alexion, based on the Reference Safety Document. The Investigator will also consult the Investigator's Brochure in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
  - There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to Alexion. However, **it is very important that the Investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to Alexion or designee.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Events and Serious Adverse Events

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Alexion to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Assessment of Causality
• If a patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide Alexion with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed eCRF. • The Investigator will submit any updated SAE data to Alexion within 24 hours of receipt of the information.

10.3.4. Reporting of Serious Adverse Events

Serious Adverse Event Reporting to Alexion or designee via an Electronic Data Collection Tool
• All SAEs will be recorded and reported to Alexion or designee immediately and within 24 hours of awareness. • The primary mechanism for reporting an SAE to Alexion or designee will be the EDC tool. • If the electronic system is unavailable at the time that the Investigator or site becomes aware of an SAE, the site will use the paper Contingency Form for SAE reporting via fax or email. Facsimile transmission or email may be used in the event of electronic submission failure. – Email: clinicalsae@alexion.com or Fax: + 1.203.439.9347 • The site will enter the SAE data into the electronic system as soon as it becomes available. • When further information becomes available, the EDC should be updated within 24 hours with the new information and an updated SAE report should be submitted to Alexion Global Drug Safety (GDS). • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form to the Alexion medical monitor by telephone.
Serious Adverse Event Reporting to Alexion or designee via Paper Safety Reporting Form
• All SAEs will be recorded and reported to Alexion or designee immediately and within 24 hours awareness. • SAEs will be reported using the Safety Reporting Form and submitted to Alexion GDS. The Investigator must complete, sign, and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy via email or facsimile to the contact information provided below: – Email: ClinicalSAE@alexion.com or Fax: + 1.203.439.9347 • Additional follow-up information, if required or available, should be entered into the eCRF and sent to Alexion GDS within 24 hours of the Investigator or study site staff becoming aware of this additional information via the reporting process outlined above. • For all SAEs, the Investigator must provide the following: – Appropriate and requested follow-up information in the time frame detailed above – Causality of the serious event(s) – Treatment of/intervention for the SAE(s) – Outcome of the serious event(s) – Medical records and laboratory/diagnostic information • All forms and follow-up information submitted to Alexion GDS MUST be accompanied by a cover page signed by the Investigator. • Paper source documents and/or reports should be kept in the appropriate section of the study file.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study drug, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the patient's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance

Before receiving study drug, female patients who consider themselves to be postmenopausal must provide evidence of postmenopause based on amenorrhea for at least 1 year prior to Day 1 visit. Confirmatory serum FSH level (> 30 IU/L) may be obtained by the Investigator at Screening. In the absence of 1 year of amenorrhea, multiple elevated FSH levels will be required.

The reason for not obtaining an FSH should be documented by the Investigator at the time of Screening.

Female patients of childbearing potential must use a highly effective or acceptable method of contraception (as defined below) starting at Screening and continuing for at least 8 months after the last dose of study drug.

Highly effective contraceptive methods include:

- Hormonal contraception associated with inhibition of ovulation
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner provided that the partner is the patient's sole sexual partner
- Sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug treatment; reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient

Acceptable contraceptive methods include:

- A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods)

The above-listed method(s) of contraception chosen for an individual patient can be determined by the Investigator with consideration for the patient's medical history and concomitant medications.

Patients with a spouse/partner of childbearing potential or a pregnant or breastfeeding spouse or partner must agree to use double barrier contraception (male condom plus appropriate barrier method for the female partner) while on treatment and for at least 8 months after the last dose of study drug. Double barrier contraception is required even with documented medical assessment of surgical success of a vasectomy.

Male patients must not donate sperm and female patients must not donate ova while on treatment and for at least 8 months after the last dose of study drug.

10.4.3. Collection of Pregnancy Information

Pregnancy data will be collected during this study for all female participants and female spouses/partners of male participants, from the first dose of study intervention. Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of drug product via semen following paternal exposure. If a female participant or a male participant's female partner becomes pregnant during the conduct of this study, the Investigator must submit the "Pregnancy Reporting and Outcome/Breastfeeding" form to Alexion GDS via facsimile or email. When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion GDS. If additional follow-up is required, the Investigator will be requested to provide the information.

Exposure of an infant to an Alexion product during breastfeeding must also be reported (via the "Pregnancy Reporting and Outcome Form/Breastfeeding") and any AEs experienced by the infant must be reported to Alexion GDS or designee via email or facsimile.

Pregnancy is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly). Elective abortions without complications should not be reported as AEs.

Any female participant who becomes pregnant while participating in the study will be discontinued from study intervention.

10.4.3.1. Male Patients With Partners who Become Pregnant

- The Investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study. This applies only to male patients who receive study drug.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to Alexion within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Alexion. Generally, the follow-up will be up to 3 months following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.4.3.2. Female Patients who Become Pregnant

- The Investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study. The initial Information will be recorded on the Pregnancy Outcome and Breastfeeding Form and submitted to Alexion within 24 hours of learning of a patient's pregnancy.
- The patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient and the neonate and the information will be forwarded to Alexion. Generally, follow-up will not be required for longer than 3 months beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study drug by the Investigator will be reported to Alexion as described in Section 10.3.4. While the Investigator is not

obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.

- Any female patient who becomes pregnant while participating in the study will discontinue study drug, and each pregnancy will be followed to term and Alexion notified regarding the outcome.

10.5. Appendix 5: El Escorial Criteria

Requirements for the Diagnosis of ALS

The diagnosis of ALS requires:

(A) The presence of:

- (A:1) evidence of **lower motor neuron (LMN)** degeneration by clinical, electrophysical or neuropathologic examination,
- (A:2) evidence of **upper motor neuron (UMN)** degeneration by clinical examination, and
- (A:3) progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination,

Together with:

(B) The absence of:

- (B:1) **electrophysiological or pathological evidence** of other disease process that might explain the signs or LMN and/or UMN degeneration, and
- (B:2) **neuroimaging evidence** of other disease process that might explain the observed clinical and electrophysiological signs

Categories of clinical diagnostic Certainty

Clinically Definite ALS is defined on clinical evidence alone by the presence of UMN, as well as LMN signs in the bulbar region and at least two spinal regions or the presence of UMN and LMN signs in three spinal regions.

Clinically Probable ALS is defined on clinical evidence alone by UMN and LMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs.

Clinically Probably ALS-Laboratory supported is defined when clinical signs of UMN and LMN dysfunction are in only one region, or when UMN signs alone are present in one region, and LMN signs defined by EMG criteria are present in at least two regions, with proper application of neuroimaging and clinical laboratory protocols to exclude other causes.

Clinically Possible ALS is defined when clinical signs of UMN and LMN dysfunction are found together in only one region or UMN signs re found alone in two or more regions; or LMN signs are found rostral to UMN signs and the diagnosis of Clinically Probable ALS-Laboratory Supported cannot be proven by evidence on clinical ground in conjunction with electrodiagnostic, neurophysiologic, neuroimaging or clinical laboratory studies. Other diagnoses must have been excluded to accept a diagnosis of Clinically Possible ALS

From:
Benjamin Rix Brooks, Robert G Miller, Michael Swash & Theodore L. Munsat (2000) El Escorial revisited: Revised criteria for the diagnosis of amyotrophic lateral sclerosis, Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders, 1:5, 293-299

10.6. Appendix 6: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R)

To be completed by Study Site

Study Number: ALXN1210-ALS-308 Subject ID: _____

Date Completed: _____ Time Completed: _____

Completed by: ☐ Evaluator (Initials) _____

The ALS Functional Rating Scale — Revised (ALSFRS-R)

1. Speech	
4	Normal speech process
3	Detectable speech disturbance
2	Intelligible with repeating
1	Speech combined with nonvocal communication
0	Loss of useful speech
2. Salivation	
4	Normal
3	Slight but definite excess of saliva in mouth; may have nighttime drooling
2	Moderately excessive saliva; may have minimal drooling
1	Marked excess of saliva with some drooling
0	Marked drooling; requires constant tissue or handkerchief
3. Swallowing	
4	Normal eating habits
3	Early eating problems — occasional choking
2	Dietary consistency changes
1	Needs supplemental tube feeding
0	NPO (exclusively parenteral or enteral feeding)
4.Handwriting	
4	Normal
3	Slow or sloppy; all words are legible
2	Not all words are legible
1	Able to grip pen but unable to write
0	Unable to grip pen
5.a Cutting food and handling utensils (patients without gastrostomy or for patients with *less than 50%* of nutrition through gastrostomy)?	
4	Normal
3	Somewhat slow and clumsy, but no help needed
2	Can cut most foods (>50%), although slow and clumsy; some help needed
1	Food must be cut by someone, but can still feed slowly
0	Needs to be fed
5.b Cutting food and handling utensils (patients with gastrostomy and *more than 50%* of nutrition through gastrostomy)?	
4	Normal
3	Clumsy but able to perform all manipulations independently
2	Some help needed with closures and fasteners
1	Provides minimal assistance to caregiver
0	Unable to perform any aspect of task
6. Dressing and Hygiene	
4	Normal function
3	Independent; Can complete self-care with effort or decreased efficiency
2	Intermittent assistance or substitute methods
1	Needs attendant for self-care
0	Total dependence

References: Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, Nakanishi A (1999) The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci 169:13–21

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Appendix 6: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) (Continued)

7. Turning in bed and adjusting bed clothes	
4	Normal
3	Somewhat slow and clumsy, but no help needed
2	Can turn alone or adjust sheets, but with great difficulty
1	Can initiate, but not turn or adjust sheets alone
0	Helpless
8. Walking	
4	Normal
3	Early ambulation difficulties
2	Walks with assistance
1	Non-ambulatory functional movement
0	No purposeful leg movement
9. Climbing stairs	
4	Normal
3	Slow
2	Mild unsteadiness or fatigue
1	Needs assistance
0	Cannot do
10. Dyspnea	
4	None
3	Occurs when walking
2	Occurs with one or more of the following: eating, bathing, dressing
1	Occurs at rest, difficulty breathing when either sitting or lying
0	Significant difficulty, considering using mechanical respiratory support
11. Orthopnea	
4	None
3	Some difficulty sleeping at night due to shortness of breath, does not routinely use more than two pillows
2	Needs extra pillows in order to sleep (more than two)
1	Can only sleep sitting up
0	Unable to sleep without mechanical assistance
12. Respiratory insufficiency	
4	None
3	Intermittent use of NIV
2	Continuous use of NIV during the night
1	Continuous use of NIV during day and night
0	Invasive mechanical ventilation by intubation or tracheostomy

References: Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, Nakanishi A (1999) The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci 169:13–21

10.7. Appendix 7: Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40)

Header to be completed by Study Site	
Study Number: ALXN1210-ALS-308	Subject ID: _____
Date Completed: _____	Time completed: _____
Completed by: ☐ Patient ☐ Study staff (Initials) _____ (Study staff only in case patient cannot complete themselves)	

ALSAQ-40

Please complete this questionnaire as soon as possible. If you have any difficulties filling in this questionnaire by yourself, please have someone help you. However it is **your** responses that we are interested in.

The questionnaire consists of a number of statements about difficulties that you may have experienced **during the last 2 weeks.** There are no right or wrong answers: your first response is likely to be the most accurate for you. **Please check the box that best describes your own experiences or feelings.**

Please answer every question even though some may seem very similar to others, or may not seem relevant to you.

All the information you provide is **confidential.**

The following statements all refer to difficulties that you may have had **during the last 2 weeks**.
Please indicate, by checking the appropriate box, how often the following statements have been true for you.

Appendix 7: Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40) (Continued)

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by checking the appropriate box, how often the following statements have been true for you.

If you cannot walk at all
please check **Always/cannot walk at all.**

How often during the last 2 weeks have the following been true?

*Please check **one box** for each question.*

	Never	Rarely	Some-times	Often	Always or cannot walk at all
1. I have found it difficult to walk short distances, e.g. around the house.	☐	☐	☐	☐	☐
2. I have fallen over while walking.	☐	☐	☐	☐	☐
3. I have stumbled or tripped while walking.	☐	☐	☐	☐	☐
4. I have lost my balance while walking.	☐	☐	☐	☐	☐
5. I have had to concentrate while walking.	☐	☐	☐	☐	☐

*Please make sure that you have checked **one box for each question** before going on to the next page.*

Appendix 7: Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40) (Continued)

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by checking the appropriate box, how often the following statements have been true for you.

If you are not able to perform the activity at all please check **Always/cannot at all**

How often during the last 2 weeks have the following been true?

Please check ***one box*** *for each question*

	Never	Rarely	Some-times	Often	Always or cannot do at all
6. Walking had worn me out.	☐	☐	☐	☐	☐
7. I have had pains in my legs while walking.	☐	☐	☐	☐	☐
8. I have found it difficult to go up and down the stairs.	☐	☐	☐	☐	☐
9. I have found it difficult to stand up.	☐	☐	☐	☐	☐
10. I have found it difficult to move from sitting in a chair to standing upright.	☐	☐	☐	☐	☐

Please make sure that you have checked ***one box for each question*** *before going on to the next page.*

Appendix 7: Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40) (Continued)

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by checking the appropriate box, how often the following statements have been true for you.

If you cannot do the activity at all
please check **Always/cannot do at all.**

How often during the last 2 weeks have the following been true?

Please check ***one box*** *for each question*

	Never	Rarely	Some-times	Often	Always or cannot do at all
11. I have had difficulty using my arms and hands.	☐	☐	☐	☐	☐
12. I have found turning and moving in bed difficult.	☐	☐	☐	☐	☐
13. I have had difficulty picking things up.	☐	☐	☐	☐	☐
14. I have had difficulty holding books or newspapers, or turning pages.	☐	☐	☐	☐	☐
15. I have had difficulty writing clearly.	☐	☐	☐	☐	☐

Please make sure that you have checked ***one box for each question*** *before going on to the next page.*

Appendix 7: Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40) (Continued)

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by checking the appropriate box, how often the following statements have been true for you.

If you cannot do the activity at all
please check **Always/cannot do at all.**

How often during the last 2 weeks have the following been true?

Please check ***one box*** *for each question*

	Never	Rarely	Some-times	Often	Always or cannot do at all
16. I have found it difficult to do jobs around the house.	☐	☐	☐	☐	☐
17. I have found it difficult to feed myself.	☐	☐	☐	☐	☐
18. I have had difficulty combing my hair or brushing and/or flossing my teeth.	☐	☐	☐	☐	☐
19. I have had difficulty getting dressed.	☐	☐	☐	☐	☐
20. I have had difficulty washing at the bathroom sink.	☐	☐	☐	☐	☐

Please make sure that you have checked ***one box for each question*** *before going on to the next page.*

Appendix 7: Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40) (Continued)

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by checking the appropriate box, how often the following statements have been true for you.

If you cannot do the activity at all
please check **Always/cannot do at all.**

How often during the last 2 weeks have the following been true?

Please check ***one box*** *for each question*

	Never	Rarely	Some-times	Often	Always or cannot do at all
21. I have had difficulty swallowing.	☐	☐	☐	☐	☐
22. I have had difficulty eating solid food.	☐	☐	☐	☐	☐
23. I have had difficulty drinking liquids.	☐	☐	☐	☐	☐
24. I have had difficulty participating in conversations.	☐	☐	☐	☐	☐
25. I have felt that my speech has not been easy to understand.	☐	☐	☐	☐	☐

Please make sure that you have checked ***one box for each question*** *before going on to the next page.*

Appendix 7: Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40) (Continued)

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by checking the appropriate box, how often the following statements have been true for you.

If you cannot do the activity at all
please check **Always/cannot do at all.**

How often during the last 2 weeks have the following been true?

Please check ***one box*** *for each question*

	Never	Rarely	Some-times	Often	Always or cannot do at all
26. I have stuttered or slurred my speech.	☐	☐	☐	☐	☐
27. I have had to talk very slowly.	☐	☐	☐	☐	☐
28. I have talked less than I used to do.	☐	☐	☐	☐	☐
29. I have been frustrated with my speech.	☐	☐	☐	☐	☐
30. I have felt self-conscious about my speech.	☐	☐	☐	☐	☐

Please make sure that you have checked ***one box for each question*** *before going on to the next page.*

Appendix 7: Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40) (Continued)

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by checking the appropriate box, how often the following statements have been true for you.

How often during the last 2 weeks have the following been true?

*Please check **one box** for each question*

	Never	Rarely	Some-times	Often	Always
31. I have felt lonely.	☐	☐	☐	☐	☐
32. I have been bored.	☐	☐	☐	☐	☐
33. I have felt embarrassed in social situations.	☐	☐	☐	☐	☐
34. I have felt hopeless about the future.	☐	☐	☐	☐	☐
35. I have worried that I am a burden to other people.	☐	☐	☐	☐	☐

*Please make sure that you have checked **one box for each question** before going on to the next page.*

Appendix 7: Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40) (Continued)

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by checking the appropriate box, how often the following statements have been true for you.

How often during the last 2 weeks have the following been true?

*Please check **one box** for each question*

	Never	Rarely	Some-times	Often	Always
36. I have wondered why I keep going.	☐	☐	☐	☐	☐
37. I have felt angry because of the disease.	☐	☐	☐	☐	☐
38. I have felt depressed.	☐	☐	☐	☐	☐
39. I have worried about how the disease will affect me in the future.	☐	☐	☐	☐	☐
40. I have felt as if I have lost my independence	☐	☐	☐	☐	☐

*Please make sure that you have checked one **box for each question.***

Thank you for completing this questionnaire.

10.8. Appendix 8: EuroQoL 5 Dimensions (EQ-5D-5L)

10.8.1. EQ-5D-5L Version for In-Clinic Use

Header to be completed by Study Site

Study Number: ALXN1210-ALS-308 Subject ID: _____

Date Completed: _____ Time Completed: _____

Completed by: ☐ Patient

Health Questionnaire

English version for the USA

Appendix 8: EQ-5D-5L Version for In-Clinic Use (Continued)

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

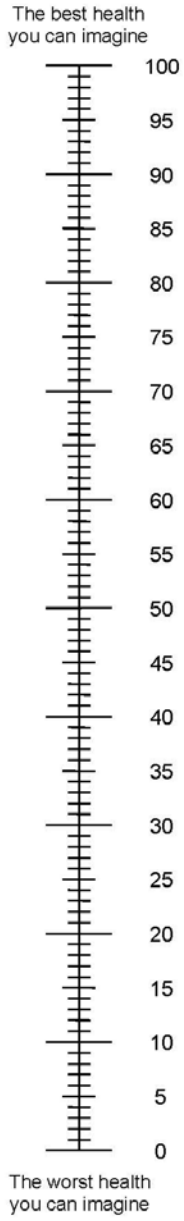
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

Appendix 8: EQ-5D-5L Version for In-Clinic Use (Continued)

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3

10.8.2. EQ-5D-5L Version for Phone Interview

To be completed by Study Site

Study Number: ALXN1210-ALS-308 Subject ID:_____

Date Completed:_____ Time Completed:_____

Completed by: ☐ Site Staff (Initials) _____

Health Questionnaire

English version for the USA

SCRIPT FOR TELEPHONE INTERVIEW

GENERAL INTRODUCTION

It is suggested that the telephone interviewer follows the script of the EQ-5D. Although allowance should be made for the interviewer's particular style of speaking, the wording of the questionnaire instructions should be followed as closely as possible. In the case of the EQ-5D descriptive system on pages 2 and 3, the exact wording must be followed.

It is recommended that the interviewer has a copy of the EQ-5D in front of him or her as it is administered over the telephone. This enables the respondent's answers to be entered directly on the EQ-5D by the interviewer on behalf of the respondent (i.e. the appropriate boxes on pages 2 and 3 are marked and the scale on page 4 is marked at the point indicating the respondent's 'health today'). The respondent should also have a copy of the EQ-5D in front of him or her for reference. If the respondent asks for clarification, the interviewer can help by re-reading the question verbatim. The interviewer should not try to offer his or her own explanation but suggest that the respondent uses his or her own interpretation.

If the respondent has difficulty regarding which box to mark, the interviewer should repeat the question verbatim and ask the respondent to answer in a way that most closely resembles his or her thoughts about his or her health today.

Appendix 8: EQ-5D-5L Version for Phone Interview (Continued)

INTRODUCTION TO EQ-5D

(Note to interviewer: please read the following)

We are trying to find out what you think about your health. I will first ask you some simple questions about your health TODAY. I will then ask you to rate your health on a measuring scale. I will explain what to do as I go along but please interrupt me if you do not understand something or if things are not clear to you. Please also remember that there are no right or wrong answers. We are interested here only in your personal view.

EQ-5D DESCRIPTIVE SYSTEM: INTRODUCTION

First I am going to read out some questions. Each question has a choice of five answers. Please tell me which answer best describes your health TODAY.

Do not choose more than one answer in each group of questions.

(Note to interviewer: it may be necessary to remind the respondent regularly that the timeframe is TODAY. It may also be necessary to repeat the questions verbatim)

EQ-5D DESCRIPTIVE SYSTEM

MOBILITY

First I'd like to ask you about mobility. Would you say that:

1. **You have no problems walking?**
2. **You have slight problems walking?**
3. **You have moderate problems walking?**
4. **You have severe problems walking?**
5. **You are unable to walk?**

(Note to interviewer: mark the appropriate box on the EQ-5D questionnaire)

SELF-CARE

Next I'd like to ask you about self-care. Would you say that:

1. **You have no problems washing or dressing yourself?**
2. **You have slight problems washing or dressing yourself?**
3. **You have moderate problems washing or dressing yourself?**
4. **You have severe problems washing or dressing yourself?**
5. **You are unable to wash or dress yourself?**

(Note to interviewer: mark the appropriate box on the EQ-5D questionnaire)

Appendix 8: EQ-5D-5L Version for Phone Interview (Continued)

USUAL ACTIVITIES

Next I'd like to ask you about your usual activities, for example work, study, housework, family or leisure activities. Would you say that:

1. **You have no problems doing your usual activities?**
2. **You have slight problems doing your usual activities?**
3. **You have moderate problems doing your usual activities?**
4. **You have severe problems doing your usual activities?**
5. **You are unable to do your usual activities?**

(Note to interviewer: mark the appropriate box on the EQ-5D questionnaire)

PAIN / DISCOMFORT

Next I'd like to ask you about pain or discomfort. Would you say that:

1. **You have no pain or discomfort?**
2. **You have slight pain or discomfort?**
3. **You have moderate pain or discomfort?**
4. **You have severe pain or discomfort?**
5. **You have extreme pain or discomfort?**

(Note to interviewer: mark the appropriate box on the EQ-5D questionnaire)

ANXIETY / DEPRESSION

Finally I'd like to ask you about anxiety or depression. Would you say that :

1. **You are not anxious or depressed?**
2. **You are slightly anxious or depressed?**
3. **You are moderately anxious or depressed?**
4. **You are severely anxious or depressed?**
5. **You are extremely anxious or depressed?**

(Note to interviewer: mark the appropriate box on the EQ-5D questionnaire)

3

Appendix 8: EQ-5D-5L Version for Phone Interview (Continued)

EQ VAS: INTRODUCTION

(Note to interviewer: If possible, it might be useful to send a visual aid (i.e. the EQ VAS) before the telephone call so that the respondent can have this in front of him or her when completing the task)

Now, I would like to ask you to say how good or bad your health is TODAY.

I'd like you to try to picture in your mind a scale that looks a bit like a thermometer. Can you do that? The best health you can imagine is marked 100 (one hundred) at the top of the scale and the worst health you can imagine is marked 0 (zero) at the bottom.

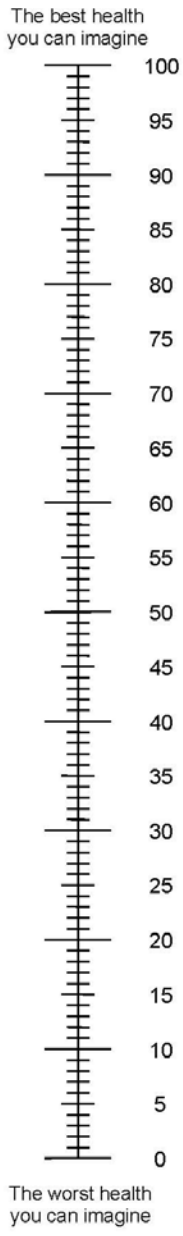
EQ VAS: TASK

I would now like you to tell me the point on this scale where you would put your health today.

(Note to interviewer: mark the scale at the point indicating the respondent's 'health today'. Now, please write the number you marked on the scale in the box below)

THE RESPONDENT'S HEALTH TODAY = ☐

Thank you for taking the time to answer these questions.



4

10.9. Appendix 9: Short Form Health Survey (SF-36)

Header to be completed by Study Site

Study Number: ALXN1210-ALS-308 Subject ID: _____

Date Completed: _____ Time Completed: _____

Completed by: ☐ Patient ☐ Study staff (Initials) _____ (Study staff only in case patient cannot complete themselves)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **<u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?**

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
▼	▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

1

Appendix 9: Short Form Health Survey (SF-36) (Continued)

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

Appendix 9: Short Form Health Survey (SF-36) (Continued)

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3

Appendix 9: Short Form Health Survey SF-36 (Continued)

6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Appendix 9: Short Form Health Survey SF-36 (Continued)

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5

Appendix 9: Short Form Health Survey SF-36 (Continued)

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

6

10.10. Appendix 10: Treatment Satisfaction Questionnaire for Medication (TSQM-9)

Header to be completed by Study Site

Study Number: ALXN1210-ALS-308 Subject ID: _____

Date Completed: _____ Time completed: _____

Completed by: ☐ Patient ☐ Study staff (Initials) _____ (Study staff only in case patient cannot complete themselves)

TSQM-9

Abbreviated Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness and convenience of the medication *over the last two to three weeks, or since you last used it*. For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

Appendix 10: Treatment Satisfaction Questionnaire for Medication (TSQM-9) (Continued)

4. How easy or difficult is it to use the medication in its current form?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

5. How easy or difficult is it to plan when you will use the medication each time?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

6. How convenient or inconvenient is it to take the medication as instructed?

☐1 Extremely Inconvenient
☐2 Very Inconvenient
☐3 Inconvenient
☐4 Somewhat Convenient
☐5 Convenient
☐6 Very Convenient
☐7 Extremely Convenient

7. Overall, how confident are you that taking this medication is a good thing for you?

☐1 Not at All Confident
☐2 A Little Confident
☐3 Somewhat Confident
☐4 Very Confident
☐5 Extremely Confident

8. How certain are you that the good things about your medication outweigh the bad things?

☐1 Not at All Certain
☐2 A Little Certain
☐3 Somewhat Certain
☐4 Very Certain
☐5 Extremely Certain

2

Appendix 10: Treatment Satisfaction Questionnaire for Medication (TSQM-9) (Continued)

9. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

3

10.11. Appendix 11: Columbia Suicide Severity Rating Scale (C-SSRS) - Screening/Baseline

To be completed by Study Site	
Study Number: ALXN1210-ALS-308	Subject ID: _____
Date Completed: _____	Time completed: _____
Completed by: ☐ Evaluator (Initials) _____	

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

C-SSRS Baseline Screening - United States/English - Mapi.
C-SSRS-BaselineScreening_AU5.1_eng-USori.doc

Appendix 11: Columbia Suicide Severity Rating Scale (C-SSRS) - Screening/Baseline (Continued)

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it... and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** ___ (*Type # (1-5)*) ___ (*Description of Ideation*) Past X Months - ***Most Severe Ideation:*** ___ (*Type # (1-5)*) ___ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	___	___
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	___	___
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	___	___
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	___	___
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	___	___

C-SSRS—Baseline/Screening (Version 1/14/09) Page 1 of 2

Appendix 11: Columbia Suicide Severity Rating Scale (C-SSRS) - Screening/Baseline (Continued)

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Lifetime	Past __ Years
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

 C-SSRS—Baseline/Screening (Version 1/14/09) Page 2 of 2

10.12. Appendix 12: Columbia-Suicide Severity Rating Scale (C-SSRS) - Since Last Visit

To be completed by Study Site	
Study Number: ALXN1210-ALS-308	Subject ID: _____
Date Completed: _____	Time completed: _____
Completed by: ☐ Evaluator (Initials) _____	

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AUS.1_eng-USorl.doc

Appendix 12: Columbia-Suicide Severity Rating Scale (C-SSRS) - Since Last Visit (Continued)

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	___
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	___
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	___
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	___
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	___

C-SSRS—Since Last Visit (Version 1/14/09) Page 1 of 2

Appendix 12: Columbia-Suicide Severity Rating Scale (C-SSRS) - Since Last Visit (Continued)

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐
Suicide:	**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

 C-SSRS—Since Last Visit (Version 1/14/09) Page 2 of 2

10.13. Appendix 13: Management of Potential Infusion-Associated Adverse Events During Study Drug Administration

Intravenous and infusion-associated reactions are a potential risk with the use of mAbs; these reactions can be nonimmune or immune-mediated (eg, hypersensitivity reactions). Signs and symptoms may include headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, hypertension, lightheadedness, hypotension, palpitations, and somnolence. Signs and symptoms of hypersensitivity or allergic reactions may include hives, swollen face, eyelids, lips, or tongue, or trouble with breathing.

All administration-, IV-, and infusion-associated reactions will be reported to the Investigator and qualified designee. The Investigator and qualified designee are responsible for detecting, documenting, and recording events that meet the definition of AE or SAE and remain responsible for following up events that are serious, considered related to the study drug, or study procedures; or that caused the patient to discontinue the study drug (Section 7).

Definitions and procedures for recording, evaluating, follow-up, and reporting AEs and SAEs are outlined in Section 10.3.

Patients who experience a reaction during the administration of study drug should be treated according to institutional guidelines.

Patients who experience a severe reaction during administration of study drug resulting in discontinuation of study drug should undergo all scheduled safety, PK, and PD evaluations required by the protocol. The Sponsor must be notified within 24 hours of any infusion reaction requiring interruption or discontinuation of study drug. All AEs that may indicate an infusion-related response will be graded according to the CTCAE v5.0 or higher.

If anaphylaxis occurs according to the criteria listed in Table 10, then administration of SC epinephrine (1/1000, 0.3 mL to 0.5 mL, or equivalent) should be considered. In the case of bronchospasm, treatment with an inhaled beta agonist also should be considered. Patients administered an antihistamine for the treatment or prevention of an infusion reaction should be given appropriate warnings about drowsiness and impairment of driving ability before being discharged from the center.

Table 10: Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:
• Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least 1 of the following: o Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) o Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
• Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): o Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips/tongue/uvula) o Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia) o Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence) o Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
• Reduced BP after exposure to known allergen for that patient (minutes to several hours): o Systolic BP of less than 90 mmHg or greater than 30% decrease from that patient's baseline

Abbreviations: BP = blood pressure; PEF = peak expiratory flow
Source: (Sampson, 2006)

10.14. Appendix 14: COVID-19 Risk Assessment

ALS is a severe disease that can cause irreversible morbidity and even mortality, if untreated. As such, and due to the limited number of available treatment options, the benefit a patient may receive from a therapeutic study is potentially significant. Ravulizumab inhibits terminal complement activation. Apart from the predictable risk of infection with Neisseria species, which is well-known and directly related to its mechanism of action, the mechanism which might lead to other serious infections including viral infections in patients treated with ravulizumab remains unclear. The Principal Investigator will therefore balance the risk/benefit considerations in their patient, taking these factors into account.

The potential risks identified and mitigation measures put in place in light of the COVID-19 pandemic are provided in Table 11.

Table 11: Potential Risks and Mitigation Measures due to COVID-19

Risks Category	Summary of Data/ Rationale for Risk	Mitigation Strategy
Potential risks		
Potentially higher risk population for SARS-CoV-2 infection	ALS is a vulnerable patient population in whom a respiratory infection may have severe consequences. It is unknown how ALS may impact the risk for COVID-19 infection.	During the time that the COVID-19 pandemic is active, Alexion will recommend that sites in a position to start the study and enroll participants follow the national and institutional guidances regarding prevention of SARS-CoV-2 infection. Additionally, during that time period, it is expected that Investigators and their staff will take all possible precautions in order to minimize a participant's potential exposure to SARS-CoV-2 infection. Depending on the site, this will consist of measures such as social distancing, temperature screening, enhanced cleaning, and use of personal protective equipment for participants, staff, and caregivers as necessary.
Healthcare institution availability for non-COVID-19 related activities	COVID-19 pandemic may impact the workload of healthcare institutions globally and may reduce staff availability to perform non-urgent activities and non-COVID-19 related activities.	During the time that the COVID-19 pandemic is active, Alexion will not open study sites or enroll new participants at sites unless the sites have the resourcing and capabilities to implement the study per protocol.

Table 11: Potential Risks and Mitigation Measures due to COVID-19

Risks Category	Summary of Data/ Rationale for Risk	Mitigation Strategy
Potential risks		
Data quality and integrity	Lack of availability of site personnel to perform study assessments and capture study specific data in a timely manner and to maintain adequate quality standards. Lack of availability of site personnel to ensure adequate and continuous chain of custody, storage conditions, and monitoring for investigational product and biological samples. Inability of study monitors and quality personnel to conduct in-person visits to exercise adequate oversight of study execution at investigational sites. Missing data (COVID-19 pandemic may impact study visit schedules, and increase missed visits and/or participant study discontinuations inadvertently resulting in missing data [eg, for protocol-specified procedures]).	During the time that the COVID-19 pandemic is active, Alexion will only open study sites that report enough personnel capacity to sufficiently conduct clinical study-related activities. During this timeframe, participants eligibility as well as site capacity will be reviewed by the site Investigator and the study Medical Monitor (or delegate) prior to Screening. Each site is also evaluated for the capacity to perform remote monitoring visits and remote source data verification. During the time that the COVID-19 pandemic is active, it will be important to capture specific information in the eCRF that explains the reason the data are missing (eg, missed study visits or participant study discontinuations due to COVID-19).

Abbreviation: ALS = amyotrophic lateral sclerosis; COVID-19 = coronavirus disease 2019; eCRF = electronic case report form; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

10.15. Appendix 15: Abbreviations

Abbreviation	Definition
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
aHUS	atypical hemolytic uremic syndrome
ALS	amyotrophic lateral sclerosis
ALSAQ-40	amyotrophic lateral sclerosis assessment questionnaire
ALSFRS-R	revised amyotrophic lateral sclerosis functional rating scale
ANCOVA	analysis of covariance
C5	complement component 5
CAFS	combined analysis of function and survival
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CNS	central nervous system
COVID-19	coronavirus disease 2019
CRF	case report form
CSF	cerebrospinal fluid
C-SSRS	Columbia-suicide severity rating scale
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation
EDC	electronic data capture
EOS	End of Study
EOT	End of Treatment
EQ-5D-5L	European Quality of Life Health 5-item questionnaire
EQ VAS	European Quality of Life Visual Analog Scale
EuroQoL	European Quality of Life
FSH	follicle stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GDS	Global Drug Safety
gMG	generalized myasthenia gravis
HHD	handheld dynamometry
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous
IVIg	intravenous immunoglobulin
KSS	King’s staging system

Abbreviation	Definition
mAb	monoclonal antibody
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
NfL	neurofilament light chain
NIV	noninvasive ventilation
NMOSD	neuromyelitis optica spectrum disorder
P	postdose (sample)
PAV	permanent assisted ventilation
PD	pharmacodynamic(s)
PE	plasma exchange
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
PP	plasmapheresis
q8w	every eight weeks
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SF-36	short form health survey
SoA	schedule of activities
SOC	System Organ Class
SVC	slow vital capacity
T	trough (predose)
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
USPI	United States Prescribing Information
VAFS	ventilation assistance-free survival
WOCBP	woman of child-bearing potential

10.16. Appendix 16: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC). Minor country-specific changes to protocol ALXN1210-ALS-308 have been implemented with country-specific amendments (Table 12). Changes from these amendments have been included in the current amendment if appropriate for global execution.

Table 12: ALXN1210-ALS-308 Protocol History

Document	Date of Issue	Overall Rationale for the Amendment
Original Protocol	26 Nov 2019	
Amendment 1 (Sweden)	09 Mar 2020	To provide a minor update on the contraception methods.
Amendment 2 (France)	08 Apr 2020	To provide minor updates on the schedule of C-SSRS screening/baseline assessment and coagulation test sample collection, as well as the treatment allocation unblinding procedure.
Amendment 2.1 (France)	25 Sep 2020	To add allowance for home and alternate clinic visits.
Amendment 3 (Germany)	14 Apr 2020	To provide a minor update on the contraception methods.
Amendment 4 (Denmark)	26 May 2020	To provide a minor update on the expected end-of-study date.
Amendment 5 (Global)	15 Oct 2020	To update study procedures: ventilator utilization at all visits, timing of PK and ADA sampling, allowance of home or alternative healthcare facility visits and home slow vital capacity (SVC) assessment, and deletion of selected Short-Form Health Survey (SF-36) assessments, selected DNA/RNA sample collections, and selected handheld dynamometry (HHD) assessments. Updates also included addition of a second methodology for the primary analysis.
Amendment 5.1 (Sweden)	04 Nov 2020	To implement changes in global Amendment 5 and retain consistency with country-specific changes detailed in Amendment 1.
Amendment 5.2 (France)	04 Nov 2020	To implement changes in global Amendment 5 and retain consistency with country-specific changes detailed in Amendments 2 and 2.1.
Amendment 5.3 (Denmark)	04 Nov 2020	To implement changes in global Amendment 5 and retain consistency with country-specific changes detailed in Amendment 4.
Amendment 5.4 (Germany)	20 Apr 2021	To implement changes in global Amendment 5, retain consistency with country-specific changes detailed in Amendment 3, and add the option for remote source data verification wherever permitted by local regulations when onsite study monitoring activities are restricted as a result of the COVID-19 pandemic.
Amendment 5.5 (United Kingdom)	27 Apr 2021	To provide guidance to study sites in the United Kingdom (UK) that reflects the current practices for recommendations related to COVID-19 vaccinations.
Amendment 6.0 (Global)		To allow patients to switch from the 10 mg/mL to the 100 mg/mL formulation of ravulizumab with no change in weight-based dosing at or after Week 52 in the OLE Period and to change from 2 to 1 planned interim analysis.

Abbreviations: ADA = antidrug antibody; COVID-19 = coronavirus disease 2019; C-SSRS = Columbia-suicide severity rating scale; DNA = deoxyribonucleic acid; OLE = Open-Label Extension; PK = pharmacokinetic(s); RNA = ribonucleic acid

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ALEXION AstraZeneca Rare Disease	**Form – Source Copy**

Clinical Note to File, Form for ALXN-SOP-0005179

Document Number	Version	Status	Effective Date
ALXN-FRM-0007589	**2.0**	**Effective**	**03 Sep 2021**

CLINICAL NOTE TO FILE

Protocol Number:	**ALXN1210-ALS-308**	
Site Number:	NA	**Subject Number:** NA
Re:	**Interim Analysis Plan Version 3.0**	

FILE
(Check at least one)

Sponsor Trial Master File: ☒	Investigator Site File: ☐	Other: ☐ Please specify:

Note to File:
Two unblinded interim analyses were planned to be conducted during the Randomized-Controlled Period. Prior to study termination, the protocol was amended (23 Jun 2021, Amendment 6) to include only 1 interim analysis, and the Interim Analysis Plan was updated accordingly (02 Jul 2021, Version 3.0). Subsequently, Amendment 6 was never implemented in the study.
The interim analysis was conducted according to the ALXN1210-ALS-308 Interim Analysis Plan V3.0 and in alignment with the protocol version that was in effect at investigative sites at the time of the analysis (15 Oct 2020, Amendment 5).

ALEXION AstraZeneca Rare Disease	**Form – Source Copy**

Clinical Note to File, Form for ALXN-SOP-0005179

Document Number	Version	Status	Effective Date
ALXN-FRM-0007589	**2.0**	**Effective**	**03 Sep 2021**

Prepared by:	PPD
Title:	**Associate Director, Biostatistics**
Signature:	PPD
Date: *(dd/mmm/yyyy)*	31-Aug-2022 | 09:45:58 EDT

REVISION HISTORY

Version No.	Change Type *(New, Revise, or Admin)*	Revision Summary	Justification
2.0	Revise	Reclassifying to Form/Template Source copy as per DOQs Form/Template project	As per Change Control PR#107515

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